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Vol. XXIII, No. 4 APRIL, 1934

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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THE 82nd ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN WASHINGTON, D. C., DURING WEEK OF MAY 7, 1934.

The 1934 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Washington.

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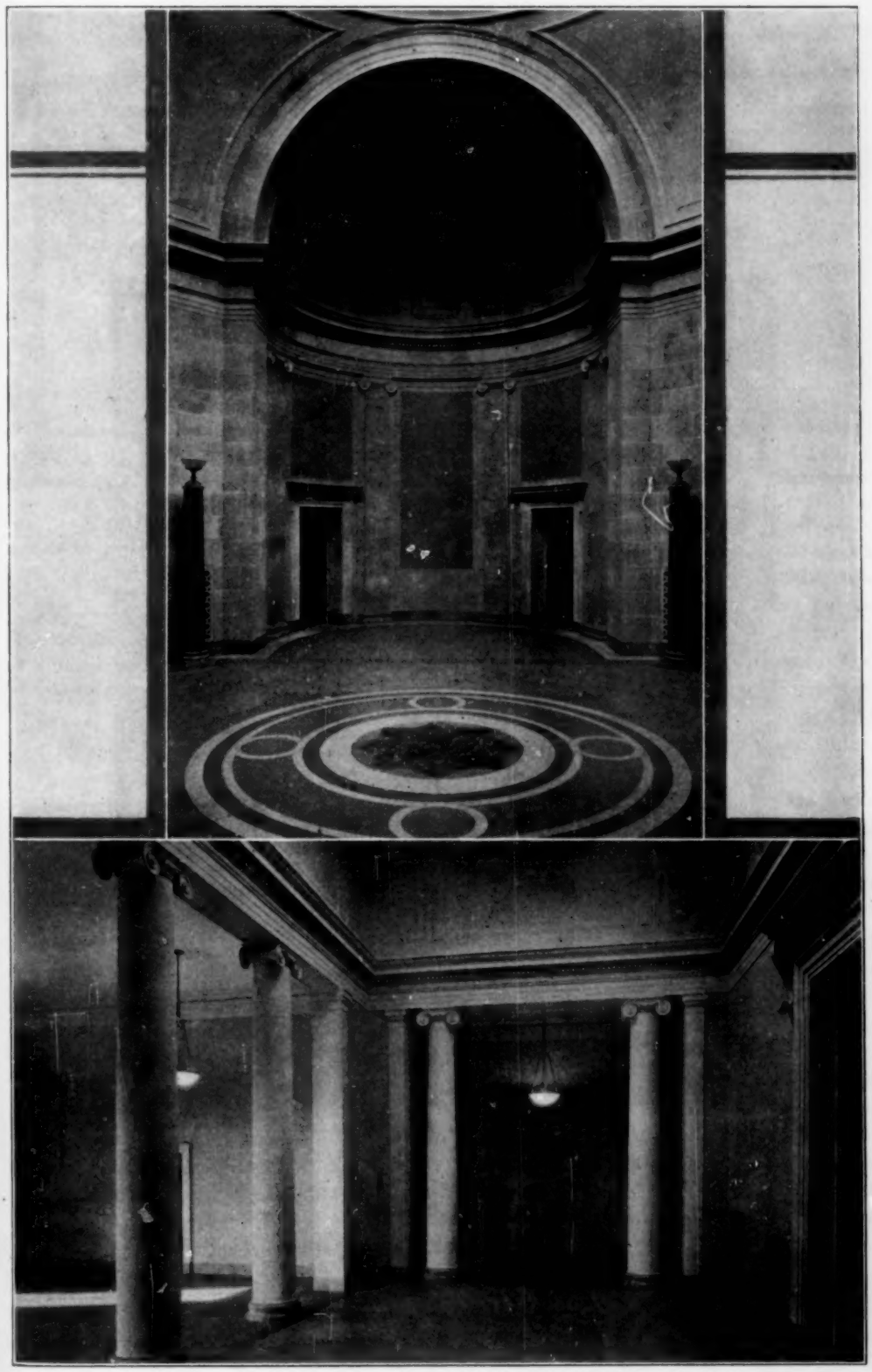
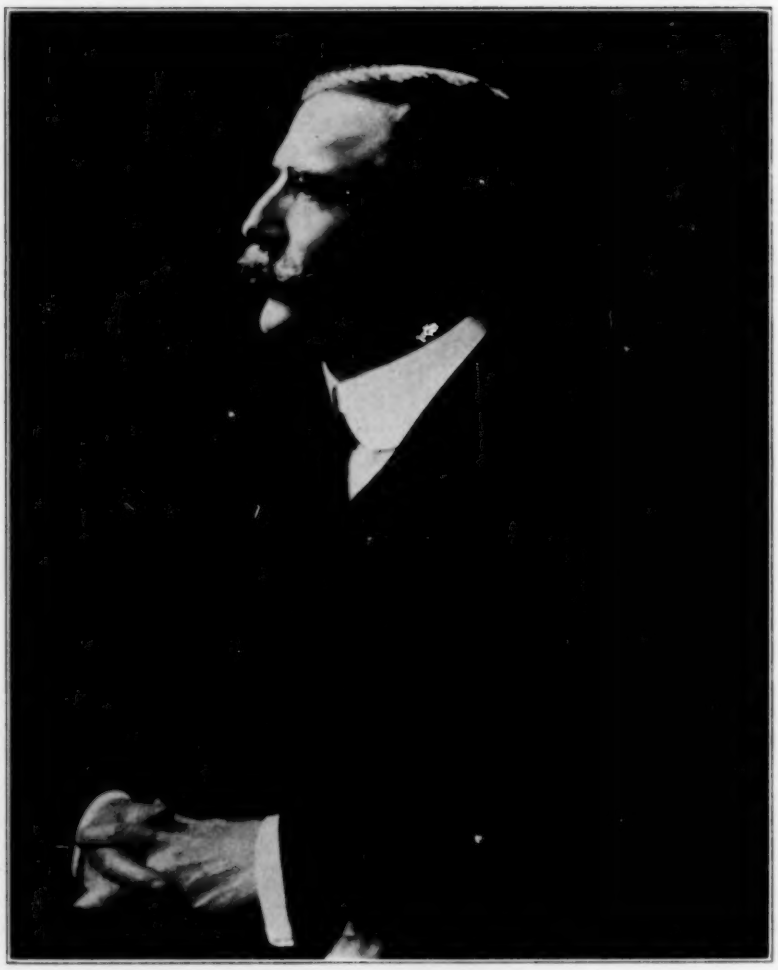


Top.—The Foyer and Alcove of the American Institute of Pharmacy. Below.—The Museum.



SIR HENRY S. WELLCOME.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXIII APRIL, 1934 No. 4

THE REMINGTON HONOR MEDALIST FOR 1934.

Sir Henry S. Wellcome, of London, England, is the Remington Medalist for 1934 and the formal award will be made during the week of May 7th in Washington. He is a native of Wisconsin; later the family moved to Minnesota where he received his early pharmaceutical training under an English chemist, manager of pharmacy in Garden City; thereafter the young man was placed in charge of the dispensing department of a pharmacy in Rochester, Minn. After several years of experience, he engaged with the late Thomas Whitfield, Chicago, and attended the Chicago College of Pharmacy; in the year following he matriculated at the Philadelphia College of Pharmacy and graduated in 1874, being a classmate of Dr. Frederick B. Power.[1] Influential factors in the beginnings of many of Mr. Wellcome's activities are referred to in the July number, 1925, of the JOURNAL, and others are noted in this sketch.

His interest in ethnological and archeological subjects had its inception in days of his frontier life and has found expression in his large undertakings and many activities; his analytical mind and powers of observation are always linked with a purpose to be of service.

In 1879, Mr. Wellcome visited South America and made a survey of the indigenous cinchona forests and reported the results of his investigations to the AMERICAN PHARMACEUTICAL ASSOCIATION, printed in its PROCEEDINGS, volume 27.

In 1887, he published "The Story of Metlakahtla," which relates to a tribe of Indians in Alaska, transformed from savagery into peaceful, industrious citizens through education and adoption of Christianity, under the leadership of William Duncan, a missionary.

Professor G. A. Reisner, distinguished archeologist of Harvard University, writing of Sir Henry's excavations in the Upper Nile region, said: "The excavations carried on by Henry Wellcome have thrown unexpected light on early Ethiopian history in this region.[2]"

[1] See Volume XI, JOUR. A. PH. A. (1922), 403.

[2] The extent of these archeological diggings may be gathered from the employment of twenty-five members of the Administration staff and 3000 native workmen.

Sir Henry's American interests are wide and varied. In 1910, when there was a strong probability of cutting down appropriations for the work of General Gorgas, it was the former's interest and valuation of tropical research that influenced the Government's continued and larger support of this important work. He is a director of the Gorgas Memorial Institute which operates scientific laboratories in Panama for research work touching cause and prevention of tropical diseases. He has established and coördinated under separate and distinct direction—The Wellcome Bureau of Scientific Research, London (1913), the Museum of Medical Science (including Tropical Medicine and Hygiene) (1914), the auxiliary Entomological Research Laboratory at Clarementon, Esher, Subrey, England (1915), the Wellcome Tropical Research Laboratories at the Gordon Memorial College, Khartoum, Anglo-Egyptian Sudan, Upper Nile, Africa (1901), and the fully equipped auxiliary Floating Tropical Research Laboratory on the Upper Nile, and its tributaries (1906).

Sir Henry has received world-wide recognition for his outstanding services to science and medicine, for his interest in missionary enterprises, for his personal work in medical research, the history of medicine and pharmacy. Apart from the research and experimental laboratories of the establishments of Burroughs Wellcome & Co., the following are some of his many enterprises:

"The Wellcome Physiological Research Laboratories," London (1894); "The Wellcome Chemical Research Laboratories," London (1896); "The Wellcome Historical Museum," London (1913). In November of 1931, in London, the cornerstone was laid for "The Wellcome Research Institution," required for coördinating and extending the activities of the Wellcome chemical and medical research laboratories and museums.

Knighthood was conferred on Dr. Wellcome by King George V in 1932, in recognition of his life-work and generous support of medical research. He is an Honorary Fellow of the Royal College of Surgeons, fellow of the Royal Society, of the Royal Society of Medicine, of the Royal Society of Tropical Medicine and Hygiene, London; Honorary Corresponding Doctor of the Ancient College of Medicine, Madrid, etc. In 1865, he was awarded the Royal Humane Society Medal for life-saving; in 1928 the University of Edinburgh conferred on him the honorary degree of Doctor of Laws. He is a member of many clubs in Great Britain and of a number in the United States—Lotus Club, New York; Cosmos Club, Washington, etc.

Mr. Wellcome became a member of the AMERICAN PHARMACEUTICAL ASSOCIATION in 1875, and has always taken an active interest in its work; in 1931, he was elected honorary president of the ASSOCIATION. Very early in the campaign for the establishment of the Headquarters he took an active part in the project evidenced by words and deeds.

Dedication ceremonies are scheduled for Wednesday morning, May 9th. The banquet and all other meetings of the Annual Convention will be held at the Shoreham, the headquarters hotel.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

PHARMACY IN HOSPITALS.

THE practice of pharmacy since it affects the public health should be regulated in the public interest and restricted to those who have been trained and licensed for this responsible work after their fitness has been proved through examination by a state agency. The AMERICAN PHARMACEUTICAL ASSOCIATION has consistently worked to put this principle into practice and to throw every protection, possible of application, around the practice of pharmacy and around the use of drugs, medicines and medical supplies by the people. A very important step in this program has just been taken and one which will have a splendid effect as it comes into general application.

The American Medical Association, through its Council on Medical Education and Hospitals, maintains a list of recognized hospitals and related institutions. One issue of its *Journal* is known as the "Hospital Number" and is devoted to information about hospitals and related institutions and to the list of registered hospitals. The "Hospital Number" for 1934 was issued on March 31st.

In the course of its work, the Council on Medical Education and Hospitals has prepared a number of "Essentials of a Registered Hospital" and admits annually to its Hospital Register only those that are found to qualify according to these essentials. The Council disclaims any legal authority over a hospital and recognizes clearly the right of those responsible for a hospital to conduct it as may seem wise to them. It does require of a hospital or related institution, desiring to have its name appear on the Hospital Register, that it be willing to comply with the principles considered necessary for such endorsement. Undoubtedly, this procedure has been effective in raising the standards of these institutions. In connection with the Essentials, the statement is made that "It is the desire of the Council to coöperate in every way for the improvement of hospital service, whereby the sick and injured may be provided with scientific and ethical medical care."

After a careful consideration of the practice of pharmacy in hospitals, the AMERICAN PHARMACEUTICAL ASSOCIATION decided that the first step toward the improvement of the pharmaceutical service was to request the inclusion among the "Essentials of a Registered Hospital" of one dealing with pharmacy. The Council on Medical Education and Hospitals approved this request, and among the Essentials as published in the recent "Hospital Number" is the following: "5. Pharmacy. The handling of drugs should be adequately supervised and should comply with state laws." Although this requirement is not as specific as it should be, it is a distinct recognition of the place of pharmacy in the hospital, represents a step in the right direction and, no doubt, will be amplified as experience is gained in its application.

With this requirement as a basis, the Boards of Pharmacy, and other institutions concerned should give hospital authorities every coöperation in making it as effective as conditions render possible. Pharmacists and their organizations should concern themselves to see that the pharmaceutical service in each hospital is adequate and that it complies with the requirements of the state laws. If the

requirements of a hospital do not justify a pharmacy in charge of a pharmacist, arrangements should be made if they do not exist, for local service.

The inclusion of this requirement is another indication of the coöperation which should exist among the public health professions. The AMERICAN PHARMACEUTICAL ASSOCIATION wishes to record its appreciation of the action of the Council on Medical Education and Hospitals which it is believed will lead to a more effective pharmaceutical service in the hospitals of our country.—E. F. K.

PERIODS IN THE HISTORY OF THE NATIONAL FORMULARY AND ITS PRECEDENTS.

THE New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION on April 9th celebrated the 50th Anniversary of the New York and Brooklyn Formulary, the precursor of the National Formulary. The former was published by a joint committee of delegates from the College of Pharmacy of the City of New York, the New York German Apothecaries' Society and the Kings County Pharmaceutical Society and entered according to Act of Congress in 1884, by the bodies named; Charles F. Schleussner, secretary of the Joint Committee, was present at the meeting held in celebration of the anniversary.

Wilbur L. Scoville, former chairman of the Committee on National Formulary, has prepared a history of the National Formulary for the ASSOCIATION, which he sketches under five divisions, including the earlier efforts to compile a formulary of unofficial preparations and the success of the New York and Brooklyn Formulary; he refers to the incorporation of the AMERICAN PHARMACEUTICAL ASSOCIATION in 1888, and details the editions of the succeeding revisions of the Formulary. The author has made an interesting and valuable contribution while recording pharmaceutical history.

During the period prior to the organization of the AMERICAN PHARMACEUTICAL ASSOCIATION, the apothecaries perfected the methods of manufacturing the galenicals and other remedial agents on which they built up their reputation and patronage; as a result of the individual studies and variety of products under the same or related names the preparations differed widely in strength, appearance and flavor. Attempts had been made to establish greater uniformity prior to the organization of the AMERICAN PHARMACEUTICAL ASSOCIATION, but the efforts of organized pharmacy were more successful and brought about greater improvements in dispensing.

"The need for a standard formulary was among the earliest considerations of the ASSOCIATION." The first record of the movement was made in the transactions of the meeting held in Cincinnati, in 1854, when it was moved that "the unofficial formulæ communicated by Messrs. Matthews of Buffalo, Cummings of Maine, and Meakim of New York and contained in the report of the executive committee be preserved by the Secretary with a view to publication when future similar publications accumulate sufficiently to justify it."

Mr. Scoville comments—"It is interesting to note that the first idea of a formulary as representing preparations used by physicians has held throughout the years without deviation and still represents the ideal of the National Formulary."

During the years following the early report heretofore referred to, dissenting views obtained relative to elixirs and many heated arguments occurred at a number of annual meetings of the ASSOCIATION.

Acting on the suggestion of J. S. Bendiner, of New York, the New York and Brooklyn Formulary was published by a joint committee of the College of Pharmacy of the City of New York, the German Apothecaries' Society of New York, and the Kings County Pharmaceutical Society. The Formulary met with favor by physicians and the desire to serve was expressed when the publishers offered to transfer the copyright to the AMERICAN PHARMACEUTICAL ASSOCIATION so that a wider use of the Formulary might be developed and its purpose extended. This acceptance necessitated that the ASSOCIATION be chartered and this was perfected in February of 1888, in Washington. It may be noted here that all of the members of the committee on the National Formulary were retail pharmacists, except Charles Rice, a hospital pharmacist, and Professor P. W. Bedford. This edition of the National Formulary was published in the volume of the PROCEEDINGS and also separately.

No attempt is made in this comment to detail the history of the National Formulary; Chairman E. N. Gathercoal has reported on the progress of National Formulary VI at recent annual meetings of the A. PH. A., and historical records are published in each edition of the National Formulary.

Quoting W. L. Scoville, a former chairman, "the primary question in National Formulary revision is, what preparations do the physicians wish to use, and no question is raised why they wish to use them. The National Formulary makes no dispute concerning the physician's therapeutic judgment. It recognizes his legal and ethical right to his own discriminating purpose, and merely aims to add the prestige of uniformity in composition and appearance and of pharmaceutical skill in compounding to the physician's desire." In medical and pharmaceutical practices the Pharmacopœia and the National Formulary serve important purposes in public health activities.

Those who laid the foundations of the standards and of the AMERICAN PHARMACEUTICAL ASSOCIATION rendered valuable services to medicine, the public, pharmacy and the drug industry in its several divisions.

The time and place for the 1934 meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION—Washington, May 7th to 12th—were selected to accord with the plans for dedicating the Headquarters Building. The occupancy of this building which with other structures that may later be erected on the site will be known as the American Institute of Pharmacy, is one of the most important events in the long history of the ASSOCIATION and marks the successful completion of the most extensive and far-reaching effort the ASSOCIATION has undertaken.

A cordial invitation is extended to our members, to every one who contributed to the Headquarters Building and others interested in the progress of Pharmacy, to attend the meeting, particularly the dedication on May 9th. The earnest desire is that no one should fail to understand that the invitation is all-inclusive of those interested.

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, L. W. Rowe, George D. Beal, F. F. Berg, C. O. Lee, E. V. Lynn, John C. Krantz, Jr., Heber W. Youngken.

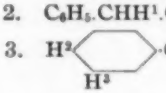
THE HYPERGLYCEMIC ACTION OF FORTY AMINES.*

BY ROBERT C. ANDERSON AND K. K. CHEN.

It is well known as a result of the work of Blum (1), Herter and Wakeman (2), Paton (3) and others that subcutaneous or intravenous injections of epinephrine are followed by a rise of blood sugar. Hyperglycemia also occurs with the homologs of epinephrine, and with tyramine and ephedrine, as shown by Morita (4), Kageyama (5), Nagel (6) and Wilson (7). It seems that pressor substances generally raise blood sugar. Nagel (6) has gone as far as to say that the elevation of the blood sugar content can be considered as a measure of the influence of a substance on the sympathetic nervous system.

In previous communications, Chen, Wu and Henriksen (8), Swanson (9) and Chen and Chen (10) reported their study on a group of amines related to ephedrine and epinephrine, mostly synthetic, with reference to their pressor action, toxicity, effect on smooth muscle organs, and other structures. The present investigation deals with the influence of forty such amines upon the blood sugar. Particular attention is drawn to any possible correlation between the pressor and hyperglycemic actions as the chemical structure varies.

The entire list of forty compounds is found in Table I. The majority of the substances are derivatives of the following three formulas:

1. $C_6H_5.CH_2.NHR$ [I]
2. $C_6H_5.CHH^1.CHR.NR^1R^2$ [II]
3.  [III]

wherein R, R^1 and R^2 = H or alkyl group, H^2 = H, OH, alkyl or alkyloxy, and H^1 and H^3 = H or OH. Four additional compounds are derivatives of indolethylamine; three, of phenyl-piperidyl-carbinols; and one, of phenyl-pyrazolone. In all, twelve primary, twenty-five secondary, two tertiary amines and one quaternary ammonium iodide are included.

Rabbits weighing approximately 2 Kg. were used for study. Aqueous solutions of the hydrochlorides of the salts were injected in the marginal vein of one ear and samples of blood were taken from that of the other. Equimolecular doses, that is, 1 cc. of a $M/10$ solution, were given, except a few, the toxicity of which was too great. In such instances, the amount was reduced. Three animals were used to study each compound. Blood samples, besides the controls, were taken 2, 5, 10, 20, 30, 40, 50 and 60 minutes after injection, and every half hour thereafter until the sugar concentration approximately returned to normal. The blood sugar was determined by the method of Hagedorn and Jensen (11). Six compounds were also studied following subcutaneous injection. The results for each were averaged and summarized in Table I.

* Scientific Section, A. PH. A., Madison meeting, 1933.

1. COMPOUNDS OF FORMULA [I].

Only two compounds, Nos. 1 and 2, belonging to the general formula, $C_6H_5.CH_2.NHR$, were studied. No. 1, $C_6H_5.CH_2.NH_2.HCl$, produced on the average a rise of 25 mg. of sugar per 100 cc. of blood, reaching its peak in 30 minutes after injection; while No. 2, $C_6H_5.CH_2.NHCH_3.HCl$, produced a rise of 18 mg., the maximum occurring in 10 minutes. In this case the primary amine seems to have a greater and more prolonged hyperglycemic action.

2. COMPOUNDS OF FORMULA [II].

Twenty-two compounds of the type, $C_6H_5.CHH^1.CHR.NR^1R^2$, were investigated. This includes the six optical isomers of ephedrine. No. 3, β-phenyl-ethylamine HCl, produced a rise of 27 mg.; while No. 4, with the OH group on the β-C atom, produced a rise of only 14 mg. No. 3 reached its peak at 40 minutes after injection, while No. 4 attained its greatest effect at the end of an hour. It is interesting to note that No. 4 was the only compound which consistently produced

TABLE I.—COMPOUNDS EXAMINED FOR HYPERGLYCEMIC ACTION.

Compound No.	Hydrochlorides of	Results. Maximal Rise of Blood Sugar mg. per 100 cc. Blood.	Time to Reach Peak after Injection (Minutes).
1	$C_6H_5.CH_2.NH_2$	25	30
2	$C_6H_5.CH_2.NHCH_3$	18	10
3	$C_6H_5.CH_2.CH_2.NH_2$	27	40
4	$C_6H_5.CHOH.CH_2.NH_2$	14	60
5	$C_6H_5.CHOH.CH_2.NHC_4H_9$	39	30
6	$C_6H_5.CHOH.CHCH_3.NH_2$	12	30
7	$C_6H_5.CHOH.CHCH_3.NH_2$ *nor-d*-Pseudoephedrine	17	30
8	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *dl*-Ephedrine	20	40
9	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *l*-Ephedrine	13	10
10	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *d*-Ephedrine	25	40
11	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *dl*-Pseudoephedrine	14	30
12	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *d*-Pseudoephedrine	20	30
13	$C_6H_5.CHOH.CHCH_3.NHCH_3$ *l*-Pseudoephedrine	30	40
14	$C_6H_5.CHOH.CHCH_3.N(CH_3)_2$ *l*-Methyl ephedrine	11	20
15	$C_6H_5.CHOH.CHCH_4.NHC_2H_5$	17	50
16	$C_6H_5.CHOH.CHCH_3.NH(CH_2.CH_2OH)$	22	50
17	$C_6H_5.CHOH.CHCH_3.NHC_3H_7$	21	50
18	$C_6H_5.CHOH.CHCH_3.NHCH(CH_3)_2$	18	30
19	$C_6H_5.CHOH.CHCH_3.NHC_4H_9$	54	30
20	$C_6H_5.CHOH.CHCH_3.NHC_5H_{11}$	40	10
21	$C_6H_5.CHOH.CHCH_3.NH(CH_2.C_6H_5)$	71	90
22	$C_6H_5.CHOH.CHCH_3.NH(CH_2.CH_2.C_6H_5)$	45	60
23	$C_6H_5.CHOH.CHC_2H_5.NHCH_3$	22	20
24	$C_6H_5.CHOH.CHC_3H_7.NHCH_3$	22	20
25	p-HO.$C_6H_4.CH_2.CH_2.NH_2$ Tyramine	17	30
26	p-HO.$C_6H_4.CHOH.CH_2.NHCH_3$ Sympatol	35	20
27	p-HO.$C_6H_4.CHOH.CHCH_2.NH_2$	28	20
28	p-$CH_3.C_6H_4.CHOH.CHCH_3.NH_2$	27	20
29	p-$CH_3O.C_6H_4.CHOH.CHCH_2.NH_2$	18	30
30	3,4-$(HO)_2.C_6H_3.CHOH.CH_2.NHCH_3$ *l*-Epinephrine	55	60
31	3,4-$(HO)_2.C_6H_3.CHOH.CHCH_3.NH_2$ 3,4-Dihydroxy-*nor*-ephedrine	45	30
32	3,4-$(HO)_2.C_6H_3.CHOH.CHCH_3.NHCH_3$ 3,4-Dihydroxy-ephedrine	37	50
33	$C_8H_6.CH_2.CH_2.NH_2$ Tryptamine	24	40
34	$C_8H_6.CH_2.CH_2.NHCH_3$ Methyl-tryptamine	29	60
35	$C_8H_6.CH_2.CH_2.N(CH_3)_2$ Dimethyl-tryptamine	35	30
36	$C_8H_6.CH_2.CH_2.N(CH_3)_3.I$ Trimethyl-tryptamine quaternary ammonium iodide	50	20
37	$C_6H_5.CHOH.CH(NH{-}CH_2{-}CH_2{-}CH_2)$ Phenyl-2-piperidyl carbinol	3	10
38	$C_6H_5.CHOH.CH(CH_2{-}NH{-}CH_2{-}CH_2)$ Phenyl-3-piperidyl carbinol	10	20
39	$C_6H_5.CHOH.CH(CH_2{-}CH_2{-}NH{-}CH_2)$ Phenyl-4-piperidyl carbinol	10	10
40	$C_6H_5.N(NH{-}CO)C.CH_2.CH_2.NH_2$ (C.CH_3) 2-Phenyl-3-methyl-5-pyrazolone-4-ethylamine	18	30

Average of three experiments.

first a fall and then a rise of blood sugar. Five minutes after injection, a fall of 9 mg. occurred. At the end of 30 minutes the blood sugar returned to its initial level, following which a rise occurred for the next 30 minutes. No. 5, a secondary amine, related to No. 4 with a butyl group replacing one H on the N atom, gave a rise of 39 mg. This agrees with the observations on other compounds of similar structure, that is, increase in the number of C atoms attached to the N atom appears to increase the hyperglycemic action. No. 6, the *dl*-product synthesized by Hartung, and No. 7, the *d*-form isolated from Ma Huang by Smith (12), differ from No. 4 in that a CH_3 group is attached to the α-C atom. The natural product produced slightly greater rise, 17 mg. as against No. 6 which caused a rise of 12 mg. Methylation on the α-C atom apparently has little influence on the hyperglycemic action since Nos. 4, 6 and 7 are nearly the same.

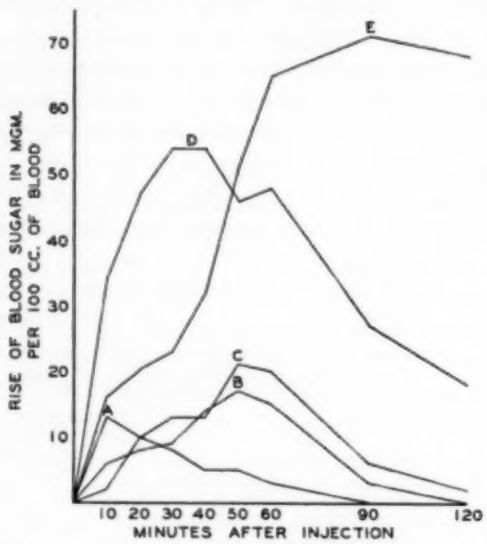


Fig. 1.—Comparison of Hyperglycemic Action of 5 Homologs.

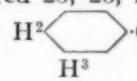
A. $C_6H_5.CHOH.CHCH_3.NHCH_3$, 1 cc. $M/10$ Solution. B. $C_6H_5.CHOH.CHCH_3.NHC_2H_5$, 1 cc. $M/10$ Solution. C. $C_6H_5.CHOH.CHCH_3.NHC_3H_7$, 1 cc. $M/10$ Solution. D. $C_6H_5.CHOH.CHCH_3.NHC_4H_9$, 1 cc. $M/10$ Solution. E. $C_6H_5.CHOH.CHCH_3.NH.CH_2.C_6H_5$, 1 cc. $M/10$ Solution.

Compounds numbered 8 to 13, inclusive, are the six optical isomers of ephedrine. Their order of activity on blood sugar is as follows: No. 9 < No. 11 < No. 12 < No. 8 < No. 10 < No. 13, the last producing a rise three times that of the first. *l*-Ephedrine, No. 9, has the least hyperglycemic action. Chen, Wu and Henriksen (8) showed that the relation in pressor action was No. 13 < No. 11 < No. 12 < No. 10 < No. 8 < No. 9, No. 9 being 35 times as strong as No. 13. Obviously, there is no correlation between the pressor and hyperglycemic actions in the optical isomers of ephedrine. No. 14, the *l*-methyl ephedrine isolated from Ma Huang by Smith (13), was found to be practically the same as *l*-ephedrine and *dl*-pseudoephedrine.

Compounds numbered 15, 17, 18, 19, 20, 21 and 22 differ from each other in the number of C atoms attached to the N atom (Table I). No. 15, the ethyl derivative, is slightly stronger than the methyl derivative (No. 9, ephedrine). The *n*-propyl derivative, No. 17, is stronger than the iso-propyl derivative, No. 18, and both in turn are stronger than the ethyl compound, No. 15. The butyl derivative, No. 19, produced a rise of 54 mg. and the amyl derivative, No. 20, showed a 40-mg. rise. However, only half the usual dose for No. 20 was given due to its high toxicity. With the addition of a benzene ring on the N atom, a further rise was observed: No. 21 caused a rise of 71 mg., and No. 22 a rise of 45 mg. Half the dosage was also used for No. 22. It appears that the hyperglycemic action increases as the number of C atoms attached to the N atom increases, as well illustrated in Fig. 1. This is contrary to

the pressor action, for Chen, Wu and Henriksen (8) showed that the pressor action decreases as the side chain on the N atom lengthens. However, when the number of C atoms linked with the α-C atom is increased, no augmentation of the hyperglycemic action occurs since Nos. 23 and 24 produced the same effect.

3. COMPOUNDS OF FORMULA [III].

Compounds numbered 25, 26, 27, 28, 29, 30, 31 and 32 are all derivatives of the general formula,  . The first five possess

an OH, CH_3 or CH_3O group in the para position, while the remaining three have OH groups in both the para and meta positions. It is difficult to say what influence a single phenolic OH exerts in a compound, for No. 25 is weaker than No. 3, but in contrast to this, No. 27 is stronger than No. 6 (Table I). The introduction of a methyl radicle to the para position seems to increase the hyperglycemic activity while a methoxy group seems to decrease it. However, only one example of each was investigated.

Owing to the fact that epinephrine is a potent substance, its dose was reduced to 0.1 cc. of a 1:1000 solution which represents approximately $^1/_{200}$ of the average amount of the preceding compounds administered. Epinephrine injected intravenously produced a rise of 55 mg. per 100 cc. Compounds numbered 31 and 32 resemble epinephrine in that they both have two OH groups in the para and meta positions. Like epinephrine, they have a high pressor action (10). With No. 31, a maximal rise of 45 mg. of blood sugar was observed following the intravenous injection of 1 cc. of 1:1000 solution. No. 32 in the dosage of 1 cc. of a 1:500 solution caused a rise of 37 mg., reaching its peak in 50 minutes. It is here that the rise of blood sugar qualitatively follows the pressor action.

TABLE II.—COMPOUNDS STUDIED BY SUBCUTANEOUS INJECTION.

Compound.	Approximate Dose. Mg. per Kg.	Rise in Blood Sugar. Intravenous.	Subcutaneous.
l-Ephedrine	20	13	0
Sympatol	20	35	0
Trimethyl-tryptamine quaternary ammonium iodide	33	50	0
l-Epinephrine	0.1	55	55
3,4-Dihydroxy-*nor*-ephedrine	1.0	45	32
3,4-Dihydroxy-ephedrine	2.0	37	90

4. ADDITIONAL COMPOUNDS STUDIED.

Of the simpler indole derivatives, the order of activity on blood sugar is dimethyl-tryptamine > methyl-tryptamine > tryptamine. In pressor action, the reverse is true (10). Trimethyl-tryptamine quaternary ammonium iodide, No. 36, was given in doses of 1 cc. of $M/40$ solution. An average rise of 50 mg. was noted. The pressor action in this case is also greater than other tryptamines (10). The

three phenyl-piperidyl carbinols and the pyrazolone, No. 40, all caused a slight elevation of blood sugar.

5. SIX COMPOUNDS STUDIED SUBCUTANEOUSLY.

Compounds numbered 9, 26, 30, 31, 32 and 36 were also studied following the subcutaneous injection. The dosage employed was the same as that used for intravenous administration. As shown in Table II, ephedrine, sympatol and trimethyl-tryptamine quaternary ammonium iodide failed to show any hyperglycemic action upon the subcutaneous injection. With epinephrine and its two homologs (Nos. 31 and 32), however, a distinct rise of blood sugar was observed. There was practically no difference between the intravenous and subcutaneous injections of epinephrine. *3,4*-Dihydroxy-*nor*-ephedrine is less effective by subcutaneous injection, but *3,4*-dihydroxy-ephedrine, on the other hand, is more than twice as active as by intravenous administration.

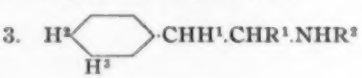
DISCUSSION.

There are few generalizations that can be made concerning the relationship between the hyperglycemic action and chemical structure. Two primary amines are stronger than two corresponding secondary amines, and two vice versa. Methylation of a compound may therefore increase or decrease the power to raise blood sugar. The lengthening of the side chain attached to the N atom is accompanied by an increase of the hyperglycemic action. The introduction of an OH group at the para position may result in an augmentation or reduction of the sugar raising property. When a compound has a structure closely similar to that of epinephrine, such as *3,4*-dihydroxy-ephedrine and *-nor*-ephedrines, the activity is at once increased. Furthermore, they become effective in influencing the blood sugar by either intravenous or subcutaneous injections.

It is evident that there is little correlation between the hyperglycemic and pressor actions; in fact, they are often diametrically opposite. For example, the pressor action diminishes and finally disappears as the length of the side chain of the N atom increases, while the reverse is true regarding the hyperglycemic effect. The order of the pressor activity of the six optical isomers of ephedrine has been found to be *l-* > *dl-* > *d-* > *d-ψ* > *dl-ψ* > *l-ψ*. On the other hand, their action on the blood sugar is almost in reverse ratio *l-ψ* > *d-* > *d-ψ* or *dl-* > *dl-ψ* > *l-*. The rise of blood sugar becomes highest when the structure of the compound approaches that of epinephrine. Even in this case the resemblance is merely qualitative. It may be interesting to point out here that only epinephrine and its close homologs raise blood sugar by subcutaneous injection.

SUMMARY.

A series of forty compounds has been studied for their hyperglycemic action. Most of them are derivatives of one of three formulas:

1. $C_6H_5.CH_2.NHR$
2. $C_6H_5.CHH^1.CHR.NR^1R^2$
3. 

wherein R, R^1 and R^2 = H or alkyl group, H^2 = H, OH, alkyl or alkyloxy, and H^1 and H^3 = H or OH. Four derivatives of indolethylamine, three those of phenyl-piperidyl-carbinols, and one that of phenyl-pyrazolone complete the list of substances investigated.

With an increase in the number of C atoms in R, R^1 and R^2, the hyperglycemic action increases.

There is little correlation between the pressor action and hyperglycemic action as the chemical structure varies. They are often diametrically opposite.

When the structure of a compound approaches that of epinephrine, a small amount will be necessary to cause a distinct response of hyperglycemia. The epinephrine homologs also raise blood sugar by subcutaneous injection.

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PANCREATIN AND ITS ASSAY.*

BY F. E. WILLSON.

The U. S. P. X has definite standards for the trypsin and amylase content of pancreatin. The B. P. 1932, also, has definite standards for these two enzymes in pancreatin and in addition has a standard for lipase content. The methods of determining tryptic and amylase content differ materially in the two pharmacopœias and also the standards set do not compare very closely. For this reason it is interesting to compare the different methods and observe some of the difficulties met with.

The U. S. P. Trypsin Method.—According to the U. S. P. X trypsin test, pancreatin should convert not less than twenty-five times its weight of casein into soluble proteoses. Therefore in this particular assay casein is used as the substrate. The actual method employed is essentially that known as the Fuld-Gross (1), (2). A 0.2% solution of casein is prepared by the use of sodium hydroxide. A definite quantity of a solution of the pancreatin to be tested is added to a definite quantity of the casein solution. Digestion is allowed to proceed for one hour's time, after

* Scientific Section, A. PH. A., Madison meeting, 1933.

which the degree of digestion of the casein is determined by the addition of an alcohol-acetic acid mixture. (U. S. P. X, page 275.)

This particular method has been the cause of considerable criticism and controversy among those concerned with the evaluation of pancreatin. The cause of variations in results obtained in carrying out this test is chiefly accounted for by the indefiniteness of the end-point. This particular difficulty was pointed out in an earlier paper (3).

Another source of variance in results may be found in the sample of powdered casein used for the substrate. There is a considerable difference in the various caseins on the market. A number of samples we have tested failed to give a clear solution in an alkaline solution. They are therefore unsuitable for use. Also several samples of casein examined have had a decided alkalinity which also would make them unsuitable for the U. S. P. test, since a more definite hydrogen-ion concentration is necessary. Furthermore with the casein supply there is a possibility of variance in moisture content of the different lots of casein.

Still another point that should be observed in carrying out trypsin assays is that the pancreatin to be tested should be left in contact with water for at least one hour before test if the full tryptic activity is to be obtained.

From these difficulties pointed out it will be observed that the present U. S. P. method is not an entirely satisfactory method.

The B. P. Trypsin Method.—The B. P. 1932 employs a modification of the Smith-Sorenson method (4) for determining the tryptic activity. Fresh milk from which the cream has been removed is used as the substrate. In other words, fresh milk furnishes the casein supply. To ensure a constant amount of casein being present, directions are given for adjustment. The milk solution is also adjusted to a definite p_H after which the pancreatin solution is added and the digestion allowed to proceed for one and a half hours at 38° to 40° C. At the end of this time the digestion mixture is rapidly cooled to 20° C. and a formol titration carried out by which the amino acids formed during the digestion are titrated. A blank is run on the milk and a boiled sample of pancreatin for correction purposes. Definite limits have been adopted in terms of $N/20$ sodium hydroxide solution for pancreatin to meet this tryptic standard.

The method, in general, seems quite satisfactory for use. Many factors which enter into the U. S. P. method are eliminated in this method. Furthermore, a definite end-point is obtained which cannot be interpreted differently by various operators.

There are several points in the B. P. method which may give a considerable variance in results. The first and most serious objection to the test is the use of fresh milk as the substrate. The opinion is expressed that milk does not furnish a substrate that is constant enough in composition to give perfectly satisfactory results. This is true even though the adjustments directed by the B. P. are carried out. The difference in the milk supply in different parts of the country was demonstrated during certain coöperative work carried out on rennin. Quite different results were obtained depending upon the section of the country the tests were carried out in and also in the source and processing the milk had gone through. This apparently was due to differences in the composition of the milk. The same conditions, it would seem, will apply to the B. P. test. Carrying out the test in

different parts of the country or even different seasons of the year are liable to give quite different results. This could be avoided by the use of powdered casein of specified purity which would have supplied a substrate of constant composition and would not have required the adjustment that the milk does before use.

The Modified Smith-Sorensen Test.—It has been pointed out that the present U. S. P. method of determining trypsin is far from satisfactory. The question then arises, how can the present method be improved or what methods are available for substitution? In our opinion the present method should be discarded and a new one substituted. In a previous paper (5) a modification of the Smith-Sorensen test was suggested. Since that time considerable work has been done on it in this laboratory as well as other laboratories. The results so far obtained indicate the method is satisfactory and at the same time not liable to the various sources of error that the present U. S. P. method contains. The method previously suggested has not been changed with the exception of a few minor points.

The adjustment of the p_H of the casein solution has been a troublesome problem in working out this method. At first a combination of phenolphthalein and brom-thymol blue was used. This was not entirely satisfactory so after considerable experimentation an aqueous solution of cresol red seemed most suitable. To give some idea of the different results obtained with different indicators two solutions of casein were prepared. One was prepared to have a p_H of not more than 8.0 while the other was prepared to have a p_H greater than 8.0. The following table gives the results obtained with various indicators.

Indicator.	Solution I.	Solution II.
Cresol Red (aqueous)	7.6	8.8
Brom-Thymol Blue (alcoholic)	6.9	7.7
Phenol Red (alcoholic)	No comparison possible	
Phenol Red B. P. (alcoholic)	..	...
Phenol Red (aqueous)	8.0+	8.4+
Thymol Blue	..	8.40
By potentiometer (quinhydrone electrode)	7.54	8.65

In determining the p_H with the various indicators the Hellige Hydrogen-Ion Comparator with the standard discs supplied for each indicator was used.

From the above table it will be observed that with both solutions the p_H obtained using an aqueous solution of cresol red approximated very closely the p_H obtained by potentiometric means.

Phenol red proved to be entirely unsatisfactory. The difficulty seemed to lie in the fact that the casein solution apparently absorbs some of the color of the indicator which gives a resulting color that does not compare with the comparison standard. This color change seems to be more pronounced with alcoholic solutions of phenol red than aqueous solutions of the indicator.

A change is suggested in the strength of the alkali to be used for titration in the Modified Smith-Sorensen method. A $N/10$ sodium hydroxide was previously suggested. Since then a $N/20$ sodium hydroxide solution has been used during certain coöperative work carried on. Lately, we have used $N/50$ sodium hydroxide which has the advantage of giving a greater volume required for neutralization and in this way reducing the experimental error. Another advantage of including $N/50$ alkali would be that the method would be more available for U. S. P. inclusion

if it were looked upon favorably. A $N/50$ sodium hydroxide is official while a $N/20$ sodium hydroxide is not.

Another point in which the proposed method could be improved upon for inclusion in the U. S. P. would be in regard to the temperature of digestion. The present method suggests a temperature of 55° C. This is the temperature used in the original Smith-Sorensen method. A temperature of 52° C. would be more suitable if the method were to be included in the next U. S. P. The reason for this is that most laboratories carrying out enzyme assays according to the present U. S. P. directions have a water-bath regulated at 52° C. for pepsin assays. Therefore if the temperature of digestion for this tryptic activity method were changed to 52° C. the same bath would be available for carrying out the digestion. This, however, would be a matter for further investigation.

The standard given for computing the tryptic activity of pancreatin samples using this method is a more or less arbitrary one based to some extent on the present U. S. P. standard. A sample that digests 25 times its own weight of casein into soluble proteoses should require on the Modified Smith-Sorensen method approximately 5.0 cc. of $N/50$ sodium hydroxide.

The feeling is expressed that using the proposed method for assay of tryptic activity a more satisfactory method of determination would be available with less divergent results being obtained by different workers.

COMPARISON OF RESULTS BY THE U. S. P., B. P. AND MODIFIED SMITH-SORENSEN METHODS.

Having considered these three methods it is of interest to see how they compare as far as actual results are concerned. Five samples of pancreatin labeled U. S. P. were procured on the market at the same time. They were all carefully assayed according to each method and the results expressed in terms of percentage of the standard adopted for each test. The results are as follows:

T.	U. S. P. Method.	B. P. Method.	Smith-Sorensen Method.
Sample A	150%	256%	160%
Sample B	220%	296%	226%
Sample C	210%	231%	234%
Sample D	105%	244%	122%
Sample E	220%	343%	234%

From these results it will be observed that with the exception of two samples the others are at least twice as strong as the U. S. P. requirements. This is not entirely surprising since the method of manufacture and the resulting activity will be controlling factors. Since there are two standards to be met by the U. S. P., the samples of pancreatin must be put on the market according to the lowest of the two activities shown to meet the U. S. P. standard. This is to say, it would be almost impossible to market a sample of pancreatin assaying exactly the U. S. P. requirements by both the tryptic standard and the amylase standard.

The B. P. standard seems a little lower than the present U. S. P. standard. From the results on the above samples no satisfactory conclusions can be obtained as to the ratio. In some cases the ratio is relatively large, whereas with Sample C the ratio is very small. The one conclusion that can be drawn, however, is that

pancreatin samples meeting the U. S. P. standard for trypsin will also meet the B. P. standard for this same activity.

The U. S. P. Amylase Assay.—The U. S. P. X states that pancreatin should convert not less than twenty-five times it weight of starch into soluble carbohydrates. In carrying out this particular assay a 3.75% starch paste is used and digestion is allowed to proceed 5 minutes with the pancreatin solution. The completeness of digestion is determined by adding a definite amount of the digestion mixture to a dilute iodine solution. If no color is produced the pancreatin meets the U. S. P. specification for amylase.

This U. S. P. method is for the most part satisfactory but there are a few points in it that may cause differences in results. One of the most important of these points concerns the preparation of the starch to be used for test. Detailed instructions are given by the U. S. P. for the starch to be used. It amounts to this, that ordinary potato starch is thoroughly washed with distilled water and dried. The moisture content is then determined and the starch used on the dry basis for the preparation of the 3.75% paste. If the U. S. P. method of washing is carried out and the washed starch dried slowly by a gradual raising of temperature of 50° C., there seems to be less difference in results than if ordinary purified potato starch is used. However, if the washed starch is immediately subjected to a temperature of 50° C. and maintained at this temperature until the greater part of the moisture is driven off, there seems to be a hardening action of some sort on the starch granules. Using starch dried in this manner invariably gives lower results of amylolytic power than when starch dried gradually or not subjected at all to washing and drying is used. There seems very little necessity of going through this washing with subsequent drying if the starch to be used has a neutral reaction. Most of the potato starch of commerce, to-day, is a highly purified product.

Another point in regard to the starch is the method of determining the moisture content. The moisture content is directed to be carried out by heating four hours at a temperature of 120° C. In determining the moisture content in this manner, with many samples of starch it has been a subject of some doubt as to whether the actual moisture content was being determined. With a number of samples, some caramelization has taken place when subjected to this temperature. It would appear that a more satisfactory method would be to dry at 100° C. possibly for a considerably greater length of time. Investigation has shown that caramelization does not take place at this temperature.

The U. S. P. directs that the equivalent amount of starch to make a 3.75% paste is mixed with boiling water and boiled for approximately 5 minutes. In preparing a starch paste in this manner, many times a satisfactory paste is not obtained. The paste produced is invariably quite thick in consistency and often very "lumpy." This increases the chance of using a paste that is not exactly 3.75% starch. This can be overcome and avoided by heating water to between 50° and 60° C. and then adding a water suspension of the starch with constant stirring. The starch mixture is then brought to boiling and boiled for 5 minutes and finally adjusted to weight. In this way a perfectly homogeneous starch paste can be prepared which is much thinner in consistency than one prepared according to U. S. P. directions. This difference in consistency makes it much easier to handle and weigh out for test.

The end-point obtained also is often a matter of doubt. This phase of the amylase test was, however, quite fully dealt with in an earlier paper (3).

The B. P. Amylase Assay.—The B. P. amylase test differs somewhat from the U. S. P. test. Instead of using ordinary potato starch, soluble starch is employed. A 1% solution of this soluble starch with 5% of sodium chloride is used in place of 3.75% starch paste. The test is carried out on a small quantity of this starch solution as compared to the U. S. P. method of using 200 Gm. of the paste. The digestion is carried out for one hour at 40° C. instead of the U. S. P. time of five minutes at 40° C. At the end of the digestion period the tubes are rapidly cooled to 20° C. and $N/50$ iodine solution added directly to the digestion tubes instead of withdrawing a definite amount and adding it to iodine solution as is the case with the U. S. P. method.

There is one serious objection to this B. P. method. The quantities of pancreatin used for tests are too small. For instance, a series ranging from 0.35 cc. to 0.65 cc. using 0.05-cc. intervals are directed to be used for tests. These quantities are much too small to warrant accurate results, especially when dealing with enzymes.

The use of soluble starch as the substrate appears to be a good one. The chance that a homogeneous mixture will not be obtained is very remote. However, no mention of moisture content of the soluble starch is made which may cause some variance in results.

The use of sodium chloride in making the starch solution is probably an unwise choice in one respect. It has been proven that sodium chloride is an activator for pancreatic amylase. Therefore the results obtained may be higher than the absolute activity of the enzyme.

Another interesting point in the B. P. directions is that on the addition of the iodine solution to the digested mixtures, the end-point in the series is that tube showing no blue color. In other words, they take as their end-point simply the complete conversion of the starch present. In the U. S. P. method the starch must be converted down through the various dextrins to the sugars. It is the dextrins that give the red and purple colors with iodine solution that the U. S. P. directs must not be present.

COMPARISON OF U. S. P. AND B. P. AMYLASE ASSAYS.

Some idea of how the U. S. P. and B. P. assay results compare can be gained from results obtained on the five samples of U. S. P. samples which were mentioned in dealing with trypsin activity. The results are as follows:

	U. S. P. Assay.	B. P. Assay.
Sample A	100%	900%
Sample B	45%	500%
Sample C	8%	110%
Sample D	80%	800%
Sample E	75%	720%

In expressing the above results a pancreatin converting 25 times its weight of starch into soluble carbohydrates was expressed as being 100%.

A similar method was used for expressing the B. P. results. Therefore in stating a sample is 900% by the B. P. what is meant is that the sample is 9 times the strength allowed by the B. P.

In looking over the above results it is interesting to note that though all five samples were labeled U. S. P. there is only one sample that actually meets the U. S. P. specifications. This does not, however, mean that the above samples were put on the market below the U. S. P. specifications. It is simply a case of dealing with an enzyme of unstable activity. The instability of pancreatic amylase is a point to which very little attention has been paid up to the present time. Whether this particular instability applies to the liquefying power as well as the starch conversion power of pancreatic amylase is an open question, it seems, at the present time. From observations made, the liquefying power does not necessarily parallel the starch conversion power. This particular point is being investigated, further, with pancreatic amylase and amylases from other sources at the present time.

From the table of results given it will also be observed that the U. S. P. standard is about 10 times that of the B. P. standard. This is not surprising since it has already been pointed out that the B. P. specifications do not require the digestion to proceed down through the dextrin stage. Therefore much higher results could be expected in relation to the U. S. P. method.

The difficulties experienced with the amylase test of the present U. S. P. is a problem to which very little attention has been paid up to the present time. How to improve upon or change the method is a matter of opinion. In the first place we feel that very few pancreatin samples on the market for any length of time will meet the U. S. P. specifications. As already pointed out this is a matter of loss of activity.

In regard to the end-point used in the present U. S. P. method it is quite liable to variance. Possibly a modification of the Fehling's solution method would prove more satisfactory as an end-point and at the same time be more accurate for the specification desired by the U. S. P., *i. e.*, conversion into "soluble carbohydrates."

The B. P. Lipase Assay.—The B. P., as already stated, has a definite standard for lipase content. The U. S. P. has up to the present time made no attempt to standardize pancreatin on this basis. The B. P. method for determination of lipase, utilizing the cream from fresh milk, is a very ingenious one and from the brief experience with it seems quite satisfactory. It is much simpler than any of the other lipase methods available and at the same time gives a very definite end-point. The results obtained on the five samples of U. S. P. Pancreatin used throughout the comparison of these different methods give the following results by the B. P. method.

	B. P. Lipase.
Sample A	129%
Sample B	107%
Sample C	63%
Sample D	100%
Sample E	83%

From these above results it will be observed that three meet the B. P. specifications while two are below the specifications.

SUMMARY.

1. The U. S. P., B. P. and Modified Smith-Sorensen assay methods for trypsin are discussed and the results by each method compared.

2. Certain changes are suggested for improving the Modified Smith-Sorensen method.

3. The U. S. P. and B. P. Amylase assay methods are discussed and compared.

4. Results of lipase content by the B. P. method are given for five samples of Pancreatin U. S. P. X examined.

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THE DETERMINATION OF STRYCHNINE AND BRUCINE AS HYDROFERROCYANIDES AND THEIR SEPARATION BY MEANS OF FERROCYANIDE.*

BY I. M. KOLTHOFF AND J. J. LINGANE.

The usual procedure for the separation of strychnine from brucine is based on the fact that brucine is fairly easily destroyed by treatment with nitric acid. In the present work it was found that this method yields approximate results only; either the brucine is not completely destroyed or on more drastic treatment part of the strychnine is decomposed also. Therefore a more exact method would be of value. It is known that ferrocyanide in acid medium gives slightly soluble crystalline hydroferrocyanides with strychnine and brucine; the former crystallizes much faster and is less soluble than the latter. Beckurts and Holtz[1] made use of this difference in behavior and titrated a strongly acid solution of the mixed alkaloids with standard potassium ferrocyanide, using ferric chloride test paper as an outside indicator. The success of the method depends on the slowness with which brucine is precipitated by the slight excess of ferrocyanide after the precipitation of strychnine is complete. The detection of the end-point, however, is not very sharp; after much practice an accuracy of about 5% could be obtained.

Gadreau[2] proposed a much more complicated method. He precipitates the strychnine and part of the brucine by addition of a large excess of ferrocyanide in weakly acid medium. The precipitate is treated with an excess of ammonia and the free alkaloids are extracted with chloroform. After evaporation of the solvent the alkaloids are dissolved in 0.1*N* hydrochloric acid and the precipitation with ferrocyanide repeated as before. The process is repeated three times and the final precipitate of strychnine hydroferrocyanide weighed after drying over sulphuric acid and finally in an oven.

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* Scientific Section, A. PH. A., Madison meeting, 1933.

[1] Beckurts and Holtz, *Pharm. Zentralhalle*, 28 (1887), 119.

[2] Gadreau, *J. pharm. chim.* [6], 4 (1927), 145.

In this study the properties of strychnine and brucine hydroferrocyanide have been investigated and a simple procedure developed for the determination of strychnine in the presence of brucine.

MATERIALS USED.

Brucine Hydrochloride.—Commercial brucine was dissolved in chloroform and treated with gaseous hydrochloric acid. The hydrochloride was allowed to crystallize and was recrystallized from alcohol containing 20% acetone. The aqueous solution of the salt was standardized by gravimetric chloride determinations. In other experiments a solution of the salt was obtained by dissolving a known amount of brucine, recrystallized from acetone and alcohol, in a slight excess of hydrochloric acid.

Strychnine Sulphate.—A Merck & Company product was used without further purification. It appeared to be the normal salt; *i. e.*, containing one molecule of strychnine per one molecule of sulphuric acid. The aqueous solution was standardized by titration with sodium hydroxide, using methyl red as indicator. In addition, the sulphate was determined gravimetrically as barium sulphate; the results obtained in the two methods agreed within 0.2%, and were 0.4% lower than those calculated from the weight of the salt taken, assuming the latter to be pure.

Potassium Ferrocyanide.—A C.P. product was twice recrystallized from water and dried over deliquescent sodium bromide. Solutions of this salt in conductivity water were used and stabilized by the addition of 0.2% of sodium carbonate.

COMPOSITION OF THE HYDROFERROCYANIDES OF STRYCHNINE AND BRUCINE.

The hydroferrocyanides of both alkaloids were prepared by precipitation from strongly acid medium (v. i.) with an excess of potassium ferrocyanide. The precipitates were washed with water and air dried. The water content was determined by heating 0.5- to 0.8-Gm. samples in a vacuum oven at 60° until constant weight was obtained. Upon continued drying at 110° no further loss in weight was found with the strychnine hydroferrocyanide. It is not recommended to heat the air-dry precipitates directly at 110°, since a decomposition, especially of the brucine compound, takes place. The hydroferrocyanide content of the precipitates was determined by titration of the aqueous suspensions with sodium hydroxide, using methyl red as indicator. The results showed that the air-dry hydroferrocyanides have the following composition:

$C_{21}H_{22}N_2O_2.H_4Fe(CN)_6.1\ H_2O$ M = 568.1
strychnine hydroferrocyanide

$C_{23}H_{26}N_2O_4.H_4Fe(CN)_6.2\ H_2O$ M = 646.2
brucine hydroferrocyanide

W. M. Cumming[1] reports a similar composition, but with two molecules of water of crystallization for the strychnine salt instead of one. However, four water determinations made by us yielded a water content between 3.1 and 3.5% (theoretical for 1 H_2O, 3.17%, for 2 H_2O, 6.15%).

SENSITIVITY OF THE PRECIPITATION OF STRYCHNINE AND BRUCINE.

The sensitivity is greatly dependent upon the acid concentration and to a lesser extent on the ferrocyanide content. The original precipitates are white, but the brucine hydroferrocyanide turns green on standing over night in acid medium. In the final procedure 1 cc. 0.5 molar potassium ferrocyanide was added to 10-cc. solution of the alkaloid salt containing the indicated amount of hydro-

[1] W. M. Cumming, *J. Soc. Chem. Ind.*, 44 (1925), 110T.

chloric acid. The results are given in Table I. It is seen that the sensitivity of the precipitation of strychnine in 0.1 to 0.5*N* hydrochloric acid is much larger than that of brucine. At these acidities 0.07-mg. strychnine can be detected in 10 cc. of solution if observed after 30 minutes of standing. The precipitation of this alkaloid, therefore, is quantitative. The sensitivity of the precipitation of brucine is the greatest in 3*N* hydrochloric acid. After 10 minutes of standing 3 mg. of brucine in 10 cc. of solution can be detected. The data in the table also indicate that the precipitation of strychnine is much faster than that of brucine.

TABLE I.—SENSITIVITY OF PRECIPITATION OF STRYCHNINE AND BRUCINE.

Concentration HCl, *N*.	Concentration Strychnine, Moles p. l.	Result.	Concentration Brucine, Moles p. l.	Result.
0	0.01	Trace ppt. after 1 hr.	0.02	No ppt. after 2 hours
0.1	0.01	Immediate ppt.	0.02	Ppt. after 25 minutes
0.1	0.004	Ppt. after 10 seconds	0.001	Ppt. after 24 hours
0.1	0.0002	Ppt. after 1–2 minutes		
0.1	0.0001	Ppt. after 3–5 minutes		
0.1	0.00004	Ppt. after 9 minutes		
0.1	0.00002	Slight ppt. after 30 minutes		
0.5	0.0001	Ppt. after 2 minutes	0.003	Ppt. after 10 minutes
0.5	0.00004	Ppt. after 9 minutes		
3			0.0008	Ppt. after 5 minutes
3			0.0006	No ppt. after 24 hours

SOLUBILITY OF STRYCHNINE AND BRUCINE HYDROFERROCYANIDES.

The solubility was determined by shaking a known weight of the salt for 45 minutes with a known volume of solvent. Longer shaking is not desirable since decomposition may take place. The solid was collected and washed quickly with small portions of alcohol and ether, and weighed after 20 minutes' drying in the air.

TABLE II.—SOLUBILITY OF STRYCHNINE AND BRUCINE HYDROFERROCYANIDE.
(TEMPERATURE 25° ± 2°.)

Solvent.	Strychnine Hydroferrocyanide Dissolved, Mg. per 100 Cc.	Brucine Hydroferrocyanide Dissolved, Mg. per 100 Cc.
Water	36	237
0.1*N* HCl	3.7	52
1*N* HCl	..	50[a]
3*N* HCl	4.2	78

[a] Temperature was 21°.

GRAVIMETRIC AND VOLUMETRIC DETERMINATION OF STRYCHNINE AS HYDROFERROCYANIDE.

Procedure.—To a measured volume of the strychnine solution water and so much hydrochloric acid is added that the concentration is 0.1 to 1*N* in a final volume of 100 cc. Five cc. 0.5 molar potassium ferrocyanide are added slowly from a pipette resulting in the rapid formation of a nicely crystalline precipitate. After 30 minutes of standing and occasional stirring the precipitate is filtered on a sintered glass crucible (1 G.–4), washed 5 to 6 times with approximately 0.1*N* hydrochloric acid, followed by two or three washings with alcohol and two or three washings with ether. Air is aspirated through for a few minutes and the crucible weighed after 20–30 minutes' standing in the air. The strychnine hydroferrocyanide $C_{21}H_{22}N_2O_2.H_4Fe(CN)_6.H_2O$ contains 58.83% strychnine.

TABLE III.—GRAVIMETRIC DETERMINATION OF STRYCHNINE.

Strychnine Taken, Gm.	HCl, *N*.	Weight Ppt., Gm.	Strychnine Found, Gm.	Error %
0.3384[a]	0.1	0.5680	0.3342	−1.3
0.3384[a]	0.1	0.5673	0.3337	−1.4
0.3384	0.1	0.5764	0.3391	+0.2
0.3384	0.1	0.5756	0.3386	+0.05
0.3384	0 1	0.5760	0.3389	+0.1
0.3384	1	0.5767	0.3393	+0.3
0.1066	1	0.1813	0.1067	+0.1
0.0677	1	0.1150	0.0677	0.0

[a] Washed with water instead of 0.1*N* hydrochloric acid.

Table III shows that the procedure gives excellent results. The concentration of the strychnine in the last example in the table was only 0.002 molar and still the theoretical yield of precipitate was found.

VOLUMETRIC DETERMINATION OF THE STRYCHNINE HYDROFERROCYANIDE.

Since the gravimetric determination of strychnine is so extremely simple, there is not much use for a volumetric determination of the precipitate. If very small quantities of strychnine have to be determined, a volumetric procedure may be of some advantage. The strychnine hydroferrocyanide can be titrated with sodium hydroxide. If methyl red is used as indicator, the end-point is determined by the following reaction:

$$BH.H_3Fe(CN)_6 + 3OH^- \longrightarrow BH^+ + Fe(CN)_6 \equiv + 3\ H_2O.$$

The color change from red to yellow is not very sharp since strychnine is a relatively weak base and the fourth ionization constant of hydroferrocyanic acid is of the order of 10^{-4}. Still the color change to yellow can be seen with an accuracy of 0.1 cc. 0.05*N* base.

The same procedure was followed as described for the gravimetric determination except that a Gooch crucible with a paper disc was used to collect the precipitate. After washing with alcohol the precipitate and paper mat were transferred to a flask and treated with 50 cc. of water and the suspension titrated with carbonate free sodium hydroxide, using methyl red as indicator. The precipitate dissolves gradually as the titration proceeds. 1 cc. 0.1*N* sodium hydroxide is equivalent to 11.14 mg. of strychnine. The data in Table IV show that the results are about 1 to 3% low. In the last example the concentration of the strychnine in the original solution was only 0.0008 molar.

TABLE IV.—VOLUMETRIC DETERMINATION OF THE PRECIPITATE.

Strychnine Taken, Gm.	HCl, *N*.	0.052*N* NaOH Used, Cc.	Strychine Found, Gm.	Error %
0.2714	1	44.91	0.2642	−2.7
0.2714	3	44.70	0.2630	−3.1
0.0678	1	11.38	0.0670	−1.2
0.0678	3	11.30	0.0665	−1.9
0.0271	1	4.38	0.0258	−4.8

GRAVIMETRIC DETERMINATION OF BRUCINE.

The same procedure was followed as described for strychnine except that the acidity was 1 to 3*N* with respect to hydrochloric acid in the final volume, filtration

made after standing for at least one hour, and the precipitate quantitatively transferred to the crucible by means of the first filtrate. If dilute hydrochloric acid is used for this purpose, the results are markedly low on account of solubility loss. After the precipitate is transferred to the crucible, it is washed 2 to 3 times with 2- to 3-cc. portions of 0.1*N* hydrochloric acid and finally with alcohol and ether. The rate of precipitation of brucine is much slower than that of strychnine; in the examples given in the table precipitation began after a few minutes' vigorous stirring. The results in Table V show that the determination of brucine as hydroferrocyanide is not as accurate as that of strychnine.

TABLE V.—GRAVIMETRIC DETERMINATION OF BRUCINE.

(0.1314 Gm. brucine taken; precipitate contains 61.00% brucine.)

HCl, *N*.	Time before Filtration, Hours.	Weight Ppt., Gm.	Brucine Found, Gm.	Error %
3[a]	1/2	0.1994	0.1216	−7.5
3[a]	1	0.1997	0.1218	−7.3
1	1	0.2103	0.1283	−2.4
3	1	0.2120	0.1293	−1.6
1	20	0.2119	0.1293	−1.6
3	20	0.2108	0.1286	−2.1

[a] Precipitate transferred to crucible with 0.1*N* HCl instead of with filtrate.

It may be mentioned that the results were 2 to 4% high if 25 to 50 cc. of 0.5 molar ferrocyanide was used instead of 5 cc. Coprecipitation of potassium does not account for these high results.

DETERMINATION OF STRYCHNINE IN THE PRESENCE OF BRUCINE.

Use has been made of the smaller solubility of strychnine hydroferrocyanide and its greater speed of precipitation as compared with the corresponding brucine compound in the separation of strychnine from brucine.

SINGLE PRECIPITATION. APPROXIMATE PROCEDURE.

The mixture of the two alkaloids is diluted with water and hydrochloric acid to a volume of 50 cc. and an acidity of 1 to 2*N*. The solution is titrated with 0.025 molar potassium ferrocyanide until all of the strychnine has been precipitated as indicated by testing with ferric chloride paper. This test is made by immersing a narrow, pointed strip of filter paper into the solution. The end of the paper which has been dipped in the solution is then torn off and a drop of ferric chloride solution placed near the rim of the wet spot. The indicator solution diffuses by capillary action and a bluish zone is formed at the junction in the presence of an excess of ferrocyanide. The end-point is not very sharp, and its detection requires some practice, an excess of 0.5 to 0.6 cc. of the ferrocyanide solution being required to make the color change visible. The mixture is allowed to stand for 10 to 15 minutes. The precipitate is then collected on a sintered glass crucible and further treated as described before in the gravimetric determination of strychnine.

The results in Table VI show that the acidity of the solution may be varied between 1 and 3*N* and that 100 mg. of strychnine can be determined in the presence

of the same amount of brucine with an accuracy of about 1 to 3%. As a rule high results are found owing to precipitation of some brucine. This error increases rapidly with increasing excess of ferrocyanide; for this reason it is safer to apply the double precipitation method as described below.

TABLE VI.—SINGLE PRECIPITATION OF STRYCHNINE IN THE PRESENCE OF BRUCINE.

(0.1066 Gm. strychine taken in all experiments. Titrated with 0.0238 molar $K_4Fe(CN)_6$. Theoretical amount of reagent required for complete precipitation of strychnine is 13.4 cc.)

Brucine Present, Gm.	HCl, *N*.	$K_4Fe(CN)_6$ Added, Cc.	Time of Standing before Filtration, Minutes.	Weight Precipitate, Gm.	Strychnine Found, Gm.	Error %
0	1	14.0	5	0.1782	0.1048	−1.7
0	1	14.2	10	0.1782	0.1048	−1.7
0	1	14.2	15	0.1788	0.1052	−1.3
0.066	1	14.0	5	0.1782	0.1048	−1.7
0.066	1	14.2	15	0.1870	0.1100	+3.2
0.066	3	14.2	15	0.1853	0.1090	+2.3
0	3	14.2	15	0.1794	0.1056	−0.9
0.131	3	14.2	15	0.1838	0.1081	+1.4
0.131	3	14.2	15	0.1864	0.1097	+2.9
0.131	3	15.0	15	0.1905	0.1121	+5.2

DOUBLE PRECIPITATION.

The mixture is brought to a volume of about 50 cc. and a hydrochloric acid concentration of about 3*N*. The solution is then titrated with 0.025 molar potassium ferrocyanide until a distinct excess (about 15 to 20%) is present as indicated by the ferric chloride test. The precipitate is filtered after 15 minutes' standing on a Gooch crucible with paper mat and washed once with a small volume of 0.1*N* hydrochloric acid. It is then transferred back into the original precipitation flask and treated with 40 to 50 cc. water and about 1*N* ammonia until the precipitate is dissolved. A slight excess of ammonia is not harmful but gives rise to the formation of the free alkaloid. Five cc. of concentrated or 10 cc. of 6*N* hydrochloric acid are added. The precipitate formed is allowed to stand for 15 minutes, collected in a sintered glass crucible (1 G.–4) and further treated as described under the gravimetric determination of strychnine.

TABLE VII.—DOUBLE PRECIPITATION OF STRYCHNINE IN THE PRESENCE OF BRUCINE.

(0.1066 Gm. of strychnine and 0.2 Gm. of brucine in all experiments.)

Excess 0.025 Molar $K_4Fe(CN)_6$ in First Ppt., %.	Second Precipitation. Volume.	HCl, *N*.	Weight Ppt., Gm.	Strychnine Found, Gm.	Error %
12	50	0.2	0.1711	0.1007	−5.5
12	50	1	0.1780	0.1047	−1.8
20	50	1	0.1832	0.1078	+1.1
20	50	1	0.1785	0.1050	−1.5
20	50	1	0.1806	0.1062	−0.4
20	125	1	0.1823	0.1072	+0.6
20	125	1	0.1806	0.1062	−0.4
20	125	1	0.1767	0.1040	−2.4
20	125	1	0.1764	0.1038	−2.6

The results in Table VII show that 100 mg. of strychnine can be determined in the presence of double the amount of brucine with an accuracy of about 1%.

It is suggested that the methods described may be advantageously applied to the direct determination of strychnine and brucine in strychnos preparations. First the sum of the two alkaloids could be determined by precipitation in acid medium with an excess of potassium ferrocyanide. The weighed precipitate then might be decomposed with ammonia and the strychnine determined as described above.

SUMMARY.

1. The sensitivity of the precipitation of strychnine and brucine in hydrochloric acid medium with hydroferrocyanide has been determined.

2. Strychnine can be determined with great accuracy by precipitation as hydroferrocyanide. The precipitate is weighed in the air-dry form. The method yields quantitative results even at great dilutions. The determination of brucine is less accurate owing to the greater solubility of its hydroferrocyanide.

3. A simple method is described for the quantitative determination of strychnine in the presence of brucine. It is based on the fact that the hydroferrocyanide of strychnine is less soluble and is formed more rapidly than that of brucine.

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THE ARSENIC CONTENT OF CHONDRUS.*

BY CHARLES H. LAWALL AND JOS. W. E. HARRISSON.

In 1931 and 1932 we conducted an investigation of the sulphur dioxide content of Chondrus, which was reported in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, Vol. XXI, No. 11, November 1932, page 1146.

In this paper we showed that sulphur dixode is not a normal constituent of natural chondrus as had been claimed, and that chondrus of European origin as sold in America was invariably contaminated with sulphur dioxide as a result of the "sulphur bleaching" process to which it is exposed before shipment to America, and that the natural chondrus shows no evidences of sulphur dioxide when subjected to tests for that adulterant by the methods of the A. O. A. C.

In view of the fact that the European samples might possibly have been bleached with arsenic containing sulphur, it seemed advisable to make a further investigation of the samples to ascertain the arsenic content.

As we had sufficient amount of all but one of the samples in question, we undertook the investigation and report the results herewith:

The method followed was that of the A. O. A. C. Methods of Analysis, page 306, 3rd Edition.

The preliminary procedure was as follows:

Ten Gm. of chondrus were digested with 25 cc. of sulphuric acid and a total of 30 cc. of nitric acid. After the organic matter had been destroyed and the digestion was complete the remaining liquid was diluted to 100 cc. and 10 cc. of this liquid was used for each determination.

The laboratory numbers, sources of the samples and sulphur dioxide content are repeated from the previous article.

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* Scientific Section, A. PH. A., Madison meeting, 1933.

The following results were obtained, the figures being the average of closely agreeing duplicates:

Lab. No.	Source.	SO_2 p. p. m.	As_2O_3 p. p. m.
33469	Wholesale Drug House	1260	6
33641	Wholesale Drug House	920	7
33642	Wholesale Drug House	4040	11
33705	Importing House "Technical"	4080	3
33706	Importing House "Medicinal"	2520	3.5
33902	Natural—before drying	none	12
33903	Natural—after first drying	none	10
33904	Natural—ready for shipment	none	8
33772	Natural—after 4 hrs.' drying	none	9
33773	Natural—after 2 days' sun-bleaching	none	10
33774	Natural—after 6 days' sun-bleaching	none	2
33775	Natural—in finished condition	none	5

Two other specimens were added to the list for investigation. One was a sample of genuine natural chondrus imported from Ireland, and the other was an Irish Moss Pudding made from this same material.

There was not sufficient of either of these samples to make sulphur dioxide determinations but the arsenic trioxide content of the chondrus itself was found to be 4 p. p. m. and of the pudding 0.11 p. p. m.

Upon studying these results it will be seen, *first*, that the arsenic content does not parallel the sulphur dioxide content; *second*, that the arsenic content of natural chondrus averages slightly higher than that of sulphur-bleached chondrus, the average for the natural being 7.5, while that of the sulphur-bleached is 6.1; *third*, that the arsenic content of every sample, whether natural or bleached is in excess of the tolerance of 1.4 p. p. m. established for arsenic in food products; and *fourth*, that the content of arsenic is not uniform, even in samples from the same locality.

In view of the wide variations in the arsenic content in samples from the same locality and in the same "collection" after the usual methods of handling, it was thought that possibly the arsenic content was due to adhering impurities and foreign matter. In further investigation of this fact one of the samples of which a considerable quantity was still available, was carefully garbled, removing all portions of shell as well as sand and adhering foreign matter. The garbled material was finely ground and subjected to examination for the arsenic content in comparison with the arsenic content of the impurities removed by garbling.

The following results were obtained:

	As_2O_3 p. p. m.
Arsenic content of original sample	12.5
Arsenic content of garbled chondrus	12.5
Arsenic content of foreign matter removed by garbling	2.0

Our conclusions are that genuine unbleached or sun-bleached chondrus contains arsenic naturally, and that the arsenic content is well in excess of the tolerance for arsenic in food products.

LABORATORIES OF LAWALL AND HARRISSON,
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COPTIS OCCIDENTALIS SALISBURY (FAM. RANUNCULACEÆ) WESTERN COPTIS. WESTERN GOLDTHREAD.[1]

BY CHARLES E. MOLLETT[2] AND B. V. CHRISTENSEN.[3]

INTRODUCTION.

Since large quantities of *Coptis occidentalis* are found growing in the mountains of northwestern Montana and northeastern Idaho, this investigation was made to determine the comparative medicinal value of this with that of the official *Coptis trifolia* found chiefly in eastern United States.

REVIEW OF LITERATURE.

The first description of the plant, which was later to bear the genus name *Coptis*, was by Halenius (probably a student of Linnæus), who placed it with the Hellebores and named it *Hellebore* or *Helleborus Trifolius* (4). It was so-called by subsequent botanists until it was separated from the Hellebore family by Salisbury, who described the plant in 1807 and created the genus *Coptis* and named it *Coptis trifolia* (4).

The species name, according to Latin nomenclature, should have been *trifoliata*, but according to present accepted procedures, the first name stands as the species name. However, in some cases as in "Flora of the Rocky Mountains and Adjacent Plains" (3) the species name *trifoliata* is still used.

The genus name *Coptis* is taken from the Greek word *Kopo*, which means "to cut," from the cut or laciniated leaves of the hardy perennial plants of the Northern Hemisphere (1). According to the Index Kewensis, in the northern hemisphere this genus at present is composed of at least ten different species. Foreign species given in "Index Kewensis" are: *anemonæfolia*, *brachypetalæ*, *orientalis*, *quinquefolia*, *japonica* and *trifoliata* (19): C. *quinquefolia* **var.** *trifoliata*, *teeta* of the *Himalayas*, *chinensis* of China, *ospriocarpa* of India, and *marii* of Formosa.

Of the North American species, Index Kewensis had, up to 1925, recognized only *trifolia*, *occidentalis*, *venosa* and *asplenifolia*.

Following the description of trifolia in 1807, by Salisbury, a new species (*C. occidentalis*) was described by Nuttall in 1838, which for some time represented the plants found growing in the northwest.

Nuttall also split the genus *Coptis*, into Coptis and *Chrysocoptis*, on the basis of one flowered and ternately divided leaves for *C. trifolia* and 2–4 flowered and pinnately divided leaves for *C. occidentalis*, as representing the new genus *Chrysocoptis*. This latter genus has not been accepted by Index Kewensis as such, but is accepted as a synonym for *Coptis occidentalis*.

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[1] Investigation carried out in Laboratory of Pharmacognosy, College of Pharmacy, University of Florida.

[2] Dean College of Pharmacy, University of Montana.

[3] Professor of Pharmacognosy and Pharmacology, University of Florida.

AUTHOR'S NOTE: More work is being done upon the plants growing in Montana and gathered in various locations and at various altitudes as well as at different times of the year, the results to be published later in an additional paper.

Nuttall further divided the species of the west into *C. occidentalis* and *C. laciniata*, on the basis of the size of the leaflets, their lobes and incisions as described by Charles V. Piper in "Flora of Washington," 1906, page 276.

The species *Coptis trifolia* is the only one which has ever been official in either the United States Pharmacopœia or the National Formulary, and is at present official in the National Formulary V under the name Coptis; Synonym, Goldthread; Botanical name, *Coptis trifolia;* Family, *Ranunculaceæ* (13). The entire plant is official (and consists usually of a nearly equal mixture of rhizomes and pressed leaves) (6).

The habit, range and habitat of *C. trifolia* is given as follows: A low perennial, growing in moist woods and swamps of northeastern United States and Canada, extending westward to Alaska (6), woods and swamps of northeastern North America, south to Maryland; mountains of North Carolina and Tennessee, and northeast Iowa (5); Northern United States and Canada, in dark shady, moist woods (8); in morasses of Canada and Siberia, Lapland and Kamchatka (4); damp mossy woods and bogs, Newfoundland to Minnesota, British Columbia and to the Alleghanies in North Carolina (7); woods and bogs of Greenland, Maryland, Minnesota, British Columbia, Alaska and Eurasia (3).

Fig. 1.—*Coptis occidentalis.* Flowering plant. Note three flowers. Collected at Noxon, Montana, May 1931.

BOTANICAL DESCRIPTION AND HABITAT.

Descriptions and ranges of *Coptis* species, said to be growing in the Northwest, are as follows (12):

Herbs perennials, low, glabrous; root stalks creeping. Leaves ternately compound. Flowers white, solitary or few, on naked scapes. Sepals 5–7, petal-like, deciduous, white or greenish. Petals 5–6, small, linear, cucullate. Stamens 10–25; follicles, 3–12. (Gk., *Kopto* to cut; from the divided leaves.)

A. Leaflets obscurely 3-lobed; sepals oval or oblong; obtuse petals enlarged at the summit. West of the Cascade Mountains and east of the Cascade Mountains.

AA. Leaflets rather deeply lobed or segmented; sepals linear or ligulate, attenuate; petals enlarged near the middle.

B. Leaves ternate.

C. All three leaflets long, petioluled leaf divisions obtuse, obtusely dentate; seed oblong. In the Cascades. East of the Cascades. (See Fig. 1. *Coptis occidentalis.*)

CC. Middle leaflet long-petioled, lateral short, petioluled leaf divisions acute, acutely dentate; seed oval. West of the Cascades. In the Cascades.—*C. laciniata.*

BB. Leaves pinnately 5-foliate. West of Cascades.—*C. asplenifolia.*

There is some doubt as to the range of *C. trifolia* (3) (12), but no disagreement as to the range of *C. occidentalis* growing only in northwestern United States.

The plants, from which the rhizomes and rootlets were used in this investigation, were found growing in damp mossy and boggy woods of western Montana. They are usually found in damp ravines and swampy woods, where the Arbor Vitæ (*Thuja plicata*) thrives. Their range extends from the Bitter Root Mountains where the woods are not so moist, to the moist woods of the northwest ridges along the Continental Divide, which pass over the boundary into Canada. *C. occidentalis* is much smaller, with thin, paper-like leaves, in its southern range in the Bitter Root Mountains, than it is on the extreme northern border extending into Canada, where it is large and coarse. The plants reach their largest size in the high, moist ravines, west of the Continental Divide, extending into Idaho.

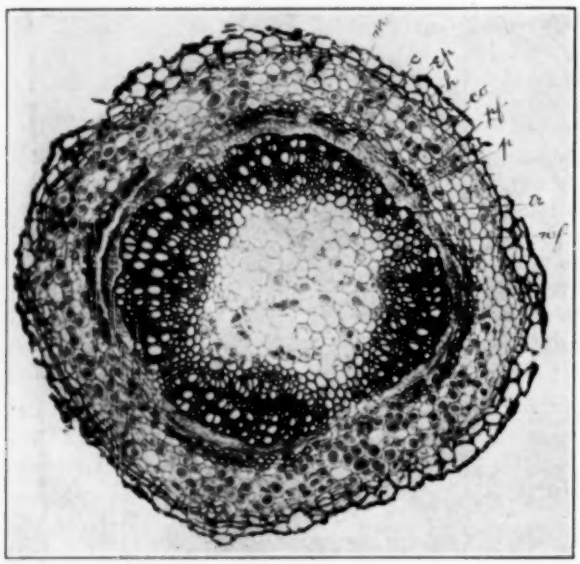

Fig. 2.—*Coptis occidentalis*. Transverse section of rhizome × 60.—*Ep*, epidermis; *h*, hypodermis; *co*, cortex; *pf*, pericyclic fibres; *p*, phloem; *c*, cambium; *tr*, tracheæ; *wf*, wood fibres in xylem; *m*, pith.

The official plant is collected while in flower, in May or June (5). Plants growing in Montana flower in April and May, putting up their pale, yellowish white flower while the ground is usually still frozen and covered with snow; this, and the pale, yellowish white color of the flowers, have given it the local name of "Snow Flowers." It is the first flower to appear in the springtime (near Noxon), in the mountains of western Montana, where the roots under investigation were obtained. Climatic conditions in Montana make it impossible to gather the rhizomes and rootlets while in flower, as it blossoms while the ground is usually frozen and covered with snow. It is not necessary to gather the entire plant of the western species as the rhizomes are twice as large as those of trifolia of the northeastern United States. Using only the rhizomes and rootlets raises the medicinal quality of the drug, as the over-ground portion of the plant contains less of the alkaloids than the rhizomes and rootlets.

This plant found growing in northwestern Montana, and northeastern Idaho corresponds with the description of *Coptis occidentalis* (Nuttall) (3), (13); and of *Chrysocoptis occidentalis* (Nuttall) (10).

EXPERIMENTAL PROCEDURE.

Pharmacognosy.—The rhizomes and rootlets were gathered in the fall, washed free from soil and leaf mold and dried. The sample was reduced to a No. 20 powder by first grinding the easily reduced portion to the required fineness in a Wyley mill and the remaining woody portion finished to the desired degree of fineness in a chaser mill, and the whole mixed thoroughly.

A portion of the powdered drug, after being irrigated with alcohol, exhibited under the

microscope, characteristics similar to those found in *Coptis trifolia*, but the cells were larger and their walls were thicker and the starch grains larger and more numerous (5*b*), (6), (13), (16).

Scrapings from the rhizomes of *Coptis occidentalis* in water mounts under the microscope (5*a*), revealed starch grains, simple or occasionally 2–3 compound, the single grains 16$^{\mu}$ in diameter and varying from spheroidal, ovoid, oblong, spindle-shaped, sub-reniform concavo convex to irregular in form with a central to occasional excentric hilum, the latter frequently 2 to several cleft to crescent shaped, the lamellæ being distinct in some of the larger grains.

Most of the individual starch grains were up to 8$^{\mu}$ in diameter.

The dried rhizomes were fixed by the usual method (5*a*), imbedded in celloidin and sections made.

Transverse sections through the internode of the rhizome showed the following histological structures:

1. A prominent large-celled epidermis with thick suberized outer walls.
2. A hypodermis of clear cells which undergo tangential division in the older rhizomes forming a cork cambium which begins to lay down subepidermal cork on its outer face.
3. A region of from 5 to 7 layers of starch and alkaloid containing cortical parenchyma cells with thin walls. The innermost layer of this region or endodermis did not differ in appearance from the other layers.
4. A pericycle of several layers containing an interrupted circle of lignified pericyclic fibre groups which alternate with starch and alkaloid containing parenchyma.

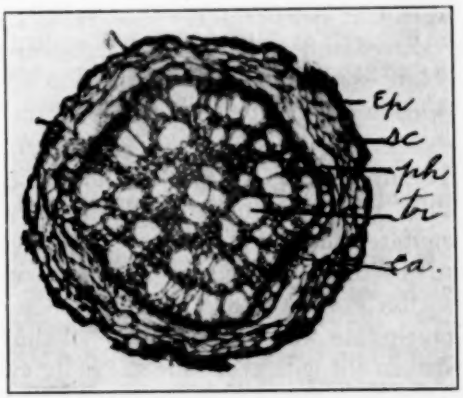

Fig. 3.—*Coptis occidentalis*. Transverse section of rootlet × 68.—*Ep*, epidermis; *sc*, secondary cortex; *ph*, phloem; *ca*, cambium, *tr*, tracheæ of xylem.

5. A circle of up to about 15 to 17 open collateral fibrovascular bundles which are separated from each other by narrow medullary rays with lignified walls. The phloem of these bundles is composed largely of sieve tubes and the xylem largely of tracheæ and wood fibres.
6. A large central pith composed of thin-walled parenchyma containing starch.

Berberine was most abundant in the parenchyma cells (5).

Longitudinal radial sections showed the tracheæ to be mostly bordered pored with circular to elliptical bordered pits. Some spiral tracheæ were evident in the protoxylem. The bordered pored tracheæ measured were up to 32 microns in diameter. Their end walls were oblique and porous.

The wood fibres and pericyclic fibres possess lignified walls with porous slits and pointed ends, the lumen being broader than the walls.

Both the cortical and pith parenchyma cells are elongated longitudinally. The chief differences noted between the sections studied of the rhizomes of this species and *C. trifolia* were:

1. The more extensive and less spongy pith in *C. occidentalis* than in *C. trifolia*.
2. The presence of a cork cambium and beginning deposition of cork tissue in *C. occidentalis* and its absence in *C. trifolia*.
3. The absence of a distinct endodermis in this species and its presence in *C. trifolia*.
4. The presence of sclerenchyma fibres in the pericycle of *C. occidentalis* and their absence of in the pericycle of *C. trifolia*.
5. The more extensive development of the xylem in *C. occidentalis* than in *C. trifolia*.
6. A larger number of root systems emanate from the rhizome of *C. occidentalis* than in *C. trifolia*.

A small sample of the drug was first extracted with ether and then with alcohol. Each of these extracts contained alkaloids according to U. S. P. X alkaloidal precipitation tests.

The marcs from the above extracts were further extracted with dilute alcohol and this extract tested for alkaloids with negative results. (The residue from the ether extraction was of a light yellow color, that from the alcohol was copious and of a dark red color.)

These preliminary tests suggested a method of analysis as follows: A sample of the powder was weighed out and placed in a Soxhlet extraction apparatus, macerated for several hours and extracted with anhydrous ether until exhausted: the extract removed and evaporated spontaneously, cooled and dried to a constant weight in a desiccator. (See Table I.) The marc from the ether extraction was removed and dried and then exhausted with absolute alcohol. The alcoholic percolate was evaporated to dryness at a low temperature on a water-bath, cooled and dried in a desiccator to constant weight. (See Table I.)

The residue from the ether extraction was of a pale greenish yellow color. The residue was dissolved in hot alcohol, thrown into ten times its volume of distilled water, acidulated with dilute hydrochloric acid and the oily resinous precipitate collected on a filter. The precipitate gave an oily stain and was resinous to the touch, completely soluble in warm sodium hydroxide solution and partly soluble in 80% alcohol, showing oil and resin. The filtrate from the oily resinous precipitate was made slightly alkaline with ammonia water and the precipitate shaken out with ether and the ether evaporated spontaneously, which left colorless crystalline plates, which gave a purplish color when first heated with sulphuric acid (5). This indicated the precipitate was probably Coptine. Further tests confirmed this and percentage yield was found to be as shown in Table I.

The residue from the alcohol extraction was dissolved in a small amount of hot water and strongly acidulated with hydrochloric acid, filtered and set aside over night. A copious deposit of bright yellow needle-shaped crystals formed. These were filtered, the mother liquor concentrated and more hydrochloric acid added and the solution heated to the boiling point and again set aside over night. The resultant crystals were added to those previously collected, the whole recrystallized from hot water and collected upon counter-balanced filters, interposed, dried in a desiccator and weighed. The crystals were found to be insoluble in ether, soluble in water and alcohol, and were of a bright yellow color and needle shaped, corresponding to Berberine hydrochloride (11). For percentage yield see Table I.

Samples of the powdered drug were placed in crucibles and incinerated according to the methods of the U. S. P. X. The ash was further treated by U. S. P. X method to determine the acid-insoluble ash. Results given in Table I.

The larger portion of the insoluble ash was found to be silica (16). The soluble portion subjected to qualitative analyses gave tests for iron, aluminum, calcium, magnesium and potassium. An aqueous extract of the powder also showed the presence of gallic and tannic acids, sugar, albumin and coloring matter.

Coptis trifolia yields 3.75 to 5.25% total ash, of which about one-tenth is silica, with iron, aluminum, calcium, magnesium and potassium present (6). (See Table I.)

Tests on the aqueous extract of *Coptis trifolia* showed the presence of tannic acid, gallic acid, starch, sugar, oil and resin, albumin and coloring matter.

TABLE I.—SHOWING COMPARATIVE ANALYSES OF *C. occidentalis* AND *C. trifolia*.

	Coptis occidentalis.	*Coptis trifolia.*
Ether extractive	2.65 %	2.275%
Alcohol extractive	19.2 %	26.27 %
Total ash	4.39 %	4.35 %
Acid-insoluble ash	0.490%	0.39 %
Coptine	0.31 %	0.3 %
Berberine	4.6 %	3.0 %

Therapeutics.—The various species of *Coptis* are said to contain from 4% to 8% of Berberine (19), to which its principal action is said to be due. It is said by recent authorities to be a simple bitter tonic, although it was formerly extensively used to heal aphthous sores in the mouth, as well as for various eye inflammations.

A 100% glycerite, made by preparing the fluidextract in the usual way, evaporating off the alcohol and making up to the original volume with glycerin, has given good results, when applied to aphthous and other scores in the mouth.

Since *C. occidentalis* contains the same constituents and about the same percentage of such constituents as *C. trifolia*, it appears logical that the medicinal effects of *C. occidentalis* should be equal and similar to those of *C. trifolia*. For this reason and because of the abundance of *C. occidentalis* in Montana and Idaho, it is suggested that *C. occidentalis* be included with *C. trifolia* in N. F. VI.

CONCLUSIONS.

1. Analysis indicates that *C. occidentalis* contains the same active constituents in about the same amounts as *C. trifolia*.

2. For this reason and because of the abundance of *C. occidentalis* in Montana and Idaho, it is suggested that *C. occidentalis* be included with *C. trifolia* in N. F. VI.

3. *C. occidentalis*, because of its abundance and convenient collection, is suggested as a commercial source of the alkaloids Coptine and Berberine in preference to *C. trifolia*.

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THE ASSAY OF HYOSCYAMUS.*

BY H. G. DEKAY[1] AND C. B. JORDAN.

Hyoscyamus has been official in the past four revisions of the U. S. Pharmacopœia, and an assay process has been described in the last three. The changes occurring in this assay have been primarily in that part of it dealing with the extraction of the alkaloids from the crude drug. In the U. S. P. VIII (first official process) the drug was macerated for 10 minutes with a mixture of 1 part of chloroform and 3 parts of ether; then ammonia water was added and the contents agitated during 1 hour. The final extraction was made from a basic mixture by the use of chloroform.

In the U. S. P. IX, the process of extraction was changed as follows: the drug was agitated during 2 hours with 300 cc. of a mixture of 1 volume of chloroform and 3 volumes of ether to which ammonia water had been added. An aliquot part of the immiscible solvent was then decanted and the assay completed as indicated in the first process. The U. S. P. X changed this to a percolation process, the same solvent being used.

Various workers encountered many difficulties in the assay of this drug with the result that a number of processes have been presented for consideration during the past decade.

Watkins and Palkin (1), workers in the Drug Control Laboratory, Bureau of Chemistry, U. S. Department of Agriculture, described a method for the assay of Hyoscyamus "which gave a yield of from two to three times as much alkaloid as that obtained by the U. S. P. IX and X methods."

In order to check the various processes for the assay of Hyoscyamus, C. B. Jordan, Dean of School of Pharmacy, Purdue University, Chairman of Subcommittee No. 6, U. S. P. Revision Committee, submitted samples from the same lot of drug in No. 60 powder to a number of experienced chemists for collaborative work. He requested that three processes be used as follows: Process No. 1 (2), the U. S. P. X process; process No. 2, which was the same except that the drug was allowed to macerate over night; process No. 3 (3), recommended by J. J. Durrett, who was, at that time, Chief, Drug Control, the U. S. Food and Drug Administration. The last was a hot extraction process very much like that used by Watkins and Palkin (1) in their work with this drug. This process required a special apparatus.

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* An abstract based upon a thesis by H. G. DeKay submitted to the Faculty of Purdue University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[1] Special worker for Sub-committee No. 6 of the U. S. P. Revision Committee.

The following results were obtained (4) in terms of percentage of total alkaloids:

Operator.	Process No. 1.	Process No. 2.	Process No. 3.
1	0.072	0.098	0.168
2	0.0381	0.0442	0.092
3	0.0306	0.0345	0.0898
4	0.0535	0.0606	0.1108
5	0.0858	0.080	0.152
6	0.0381	0.0462	0.0722
7	0.072	0.063	0.131
8	0.088	0.109	0.137
9	0.090	0.1014	0.1014

The collaborators pointed out that in processes No. 1 and No. 2 difficulty was encountered during the acid extraction because of coloring matter which could not be removed by filtering. They suggested that in process No. 3 the small amount of alcohol used could explain the increase in yield of the alkaloid. They also stated that it was extremely awkward to use the special apparatus for maceration and extraction and that the extractive was highly colored, making the end-point reading difficult.

These reports indicated that it was difficult to obtain concordant results by either the first or the second processes and that the agreement in the third was far from satisfactory. It is possible that the personal factor plays an important part; if so, an assay process should be devised that would reduce this factor to a minimum.

The chairman of the Revision Committee received a definite recommendation from J. J. Durrett (3) regarding this assay process and the purity rubric of this drug. It was passed on to the chairman of the Sub-committee on Crude Drug Assay. The above-quoted results indicated to him that the whole question should be carefully studied, and this explains the assignment of the problem to H. G. DeKay, who had been working on the assay of Hyoscyamus for about twelve months.

We believed that the higher results obtained by Watkins and Palkin, which we assumed was the basis for J. J. Durrett's recommendation, could be due to one or more of the following reasons: *1.* Failure of the U. S. P. X process to extract all of the alkaloid, presumably the idea of Watkins and Palkin; *2*, the presence in the drug of bases other than alkaloids; *3*, the decomposition of the alkaloids during the assay process; or *4*, the formation of some alkaloidal hydrochloride in the evaporation with chloroform which would indicate a low yield of alkaloid. Therefore, any successful study of this problem should cover these four points.

The following determinations upon the pure alkaloids had been completed previous to H. G. DeKay's special assignment to the problem.

I. TO DETERMINE THE STABILITY OF ATROPINE AND HYOSCYAMINE.

Experiments under A and B were performed by H. G. DeKay, A. C. Smith and C. N. Sprankle, graduate students at Purdue University.

A. TO DETERMINE THE EFFECT OF HEAT ON THE ALKALOIDS.

Experiment 1. Four samples of pure alkaloid were dried at 80° C. for 1 hour without loss.

Experiment 2. The pure alkaloids were dissolved in 2% sulphuric acid, the solution was made basic with ammonia T.S. and extracted with chloroform. The chloroform was evaporated to about 2 cc. on a water-bath and treated as follows, before completing the assay:

	Atropine.			Hyoscyamine.		
	Assays.	Used, Gm.	Recovered, Gm.	Assays.	Used, Gm.	Recovered, Gm.
A. Standard acid was added and the assay completed	8	0.0398	0.0472	2	0.0349	0.0354
B. Dried in a current of air at 40° C.	3	0.0486	0.0472	3	0.0328	0.0328
C. Repeat B and dry the residue 48 hours in a desiccator	2	0.1070	0.1027	2	0.0455	0.0443
D. Evaporate to dryness and heat 5 minutes	5	0.0361	0.0371	5	0.0351	0.0340
E. Repeat D except heat 30 minutes	5	0.0349	0.0349	3	0.0351	0.0300

Conclusion: From the above experiments it is evident that the heating of chloroform solutions of the pure alkaloids at water-bath temperatures does not cause any decomposition.

B. TO DETERMINE THE EFFECT OF CHLOROFORM UPON THE ALKALOIDS.

Experiment 1. The pure alkaloids were dissolved in chloroform and the solution evaporated to 2 cc. and treated as follows, before completing the assay:

	Atropine.			Hyoscyamine.		
	Assays.	Used, Gm.	Recovered, Gm.	Assays.	Used, Gm.	Recovered Gm.
A. Evaporated to dryness on a water-bath and heated (1) 1 hour	2	0.1609	0.1591	2	0.1040	0.1032
(2) over night	2	0.1609	0.1591	2	0.1040	0.1032
B. The assay completed	5	0.0422	0.0435	5	0.0301	0.0297
C. Evaporated to dryness on a water-bath, (1) heated 15 minutes				2	0.0385	0.0411
(2) heated 30 minutes				2	0.0408	0.0411
(3) heated 1 hour				2	0.0413	0.0410
D. Evaporated to dryness in a current of air, dried in a desiccator for 48 hours	3	0.0239	0.0242			

Experiment 2. The alkaloids were dissolved in chloroform and allowed to remain in the solvent (A) 12 hours and (B) 24 hours, respectively, before completing the assay.

		Gm.	Gm.		Gm.	Gm.
(A)	3	0.0419	0.0421	3	0.0301	0.0304
(B)	3	0.0431	0.0431	3	0.0200	0.0202

Conclusion: The above experiments indicate that no hydrochlorides of the alkaloids are formed when their chloroform solutions are evaporated to dryness at water-bath temperatures.

C. TO DETERMINE THE EFFECT OF ASSAY PROCESSES ON THE ALKALOIDS.

Experiment 1. (A) The U. S. P. X assay process for Hyoscyamus was followed, atropine instead of the crude drug being used. (B) Experiment A was repeated except that the final chloroform extract was dried in a current of air at 40° C. and the assay completed.

(A) Results of 2 samples: Used 0.0480 Gm. Recovered 0.0502 Gm.
(B) Results of 2 samples: Used 0.0463 Gm. Recovered 0.0451 Gm.

Experiment 2. Pure atropine was extracted with ammonia water, alcohol and ether in a Soxhlet apparatus for 2 hours, (A) the assay was completed. (B) The final chloroform extract was evaporated to dryness, placed in a desiccator over night and the assay completed.

(A) Results of 2 samples: Used 0.0481 Gm. Recovered 0.0488 Gm.
(B) Results of 2 samples: Used 0.0422 Gm. Recovered 0.0423 Gm.

Experiment 3. (A) An exhausted drug was fortified with equal parts of pure atropine and hyoscyamine, placed in a Soxhlet apparatus and assayed according to the process recommended by J. J. Durrett. (B) The above experiment was repeated, the final chloroform solution was evaporated to dryness on a water-bath, taken up in chloroform and again dried. This was repeated two more times before completing the assay.

(A) Results of 2 samples: Used 0.021 Gm. Recovered 0.0236 Gm.
(B) Results of 2 samples: Used 0.021 Gm. Recovered 0.0215 Gm.

Experiment 4. A definite weight of a mixture of equal parts of pure alkaloids was added to the crude drug and then assayed by the above method.

Results from 3 samples: Added alkaloid 0.0207 Gm. Recovered 0.0194 Gm.

Experiment 5. Experiment 4 was repeated to the point where the final chloroform solution is evaporated to low volume. This extract was evaporated to dryness on a water-bath, redissolved in chloroform and again dried; this was repeated two more times and the assay was completed.

Results from 2 samples: Added alkaloid 0.020 Gm. Recovered 0.0173 Gm.

Conclusion: A careful study of the above experiments indicates:

1. That the alkaloids of Hyoscyamus undergo no change during the regular assay process; *2*, that the alkaloids may be heated at water-bath temperatures without danger of decomposition; *3*, that no hydrochlorides of the alkaloids are formed when chloroform solutions of them are evaporated to dryness; and *4*, that the assay process recommended by J. J. Durrett extracts some volatile base.

Schou and Bjerregaard (5), while working upon sterilization of solutions, found that solutions of atropine could be heated at 120° C. over a period of 20 minutes without danger of decomposition.

Five experiments were completed to determine whether ammonia contaminates the residues from the assay processes. It is apparent that any ammonia which is carried over by the chloroform in the final extraction is eliminated in the evaporation process.

Our results corroborate the work of Watkins and Palkin on the stability of these alkaloids and verifies their conclusion that the residues after shaking out and drying are not contaminated with ammonia.

II. EXPERIMENTS ON POWDERED HYOSCYAMUS.

A 75-pound lot of Hyoscyamus in No. 60 powder was obtained from Eli Lilly & Company for this work. The drug was ground and mixed by the Company. Ash determinations were made with the following results:

Total Ash.	Acid-Insoluble Ash.
23.25%	8.71%
23.29%	8.65%
23.20%	8.67%
23.17%	8.87%

Qualitative inorganic analysis upon the ash showed the presence of potassium, sodium, ammonia and iron as the sulphates, nitrates and chlorides. There were traces of aluminum.

Assay Experiments.—Experiment 1. A sample of drug was subjected to the U. S. P. X process of extraction, stronger ammonia water being used. The extract was subjected to the purification process recommended by Watkins and Palkin as follows: The extract was evaporated to low volume, 10 cc. of 0.05*N* sulphuric acid and 5 cc. of water added and the evaporation continued until the odor of ether had disappeared. The acidified liquid was decanted into a 50-cc. volumetric flask. The residue remaining in the flask was dissolved with chloroform, 5 to 10 cc. of acidulated water added and the chloroform removed by heating. The contents of the original flask were poured into the volumetric flask, which was cooled and made up to volume. The mixture was filtered, the first few cc.'s rejected, an aliquot part collected, made basic with ammonia water, shaken out with chloroform and the assay completed with the following results:

1. 0.079%
2. 0.073%

The titrated mixtures gave positive results for primary amines by the isonitrile reaction.

Experiment 2. Samples were subjected to the U. S. P. X assay process modified by macerating over night and by the use of stronger ammonia water with results as follows:

1. 0.0663%	7. 0.073 %
2. 0.079 %	8. 0.0763%
3. 0.057 %	9. 0.066 %
4. 0.082 %	10. 0.0731%
5. 0.0834%	11. 0.0761%
6. 0.0733%	12. 0.0633%
	Average 0.073 %

The titrated mixtures gave positive results by the isonitrile test.

Experiment 3. Samples of the drug were subjected to the U. S. P. X assay process with the Watkins and Palkin purification process being used in place of shaking out with dilute sulphuric acid.

1. 0.110%	7. 0.087 %	13. 0.122%
2. 0.093%	8. 0.107 %	14. 0.114%
3. 0.092%	9. 0.083 %	15. 0.107%
4. 0.104%	10. 0.109 %	16. 0.113%
5. 0.101%	11. 0.088 %	17. 0.112%
6. 0.094%	12. 0.1225%	Average 0.103%

Positive results were obtained by the isonitrile test.

Experiment 4. Samples of the drug were subjected to Soxhlet extraction after one-hour maceration with U. S. P. solvents and then the assay completed by the W. & P. process.

1. 0.1025%
2. 0.1001%

Positive results were obtained by the isonitrile test.

Experiment 5. The above experiment was repeated except that the residues were dried, before the assay was completed, as follows: (A) On the water-bath; (B) in an oven at 80° for 1 hour.

(A.)		(B.)
1. 0.0627%	4. 0.0428%	1. 0.0319%
2. 0.0564%	5. 0.0440%	2. 0.0424%
3. 0.0553%	Average 0.0522%	Average 0.0371%

The above gave faint isonitrile tests.

Experiment 6. Lots of drug were macerated over night with stronger ammonia water and the U. S. P. solvent, and percolated according to the U. S. P. X process. Then the percolate was subjected to the W. & P. purification process. Later the marc from each sample was extracted in a Soxhlet, alcohol being used as a solvent. Additional basic material was secured.

	Assay.	Basic Constituent Extracted by Alcohol.	Total.
1.	0.122%	0.0178%	0.140%
2.	0.114%	0.021 %	0.135%
3.	0.113%	0.019 %	0.132%

The titrated mixtures gave positive isonitrile tests.

Experiment 7. Three samples were assayed by the W. & P. process, their special apparatus being used.

1. 0.100 %
2. 0.102 %
3. 0.1047%

Experiment 8. Samples of drug were assayed by the W. & P. process, the solvents recommended by them being used, were then macerated over night and were extracted in a Soxhlet apparatus.

1. 0.136%	7. 0.125 %	13. 0.146%
2. 0.132%	8. 0.109 %	14. 0.127%
3. 0.155%	9. 0.1167%	15. 0.135%
4. 0.127%	10. 0.1205%	16. 0.127%
5. 0.120%	11. 0.1025%	17. 0.125%
6. 0.125%	12. 0.135 %	Average 0.127%

All of these titrated residues gave positive results by the isonitrile test.

Experiment 9. Samples of drug were macerated over night with ether-alcohol solvent and stronger ammonia water, then percolated according to the U. S. P. X using ether and the percolate subjected to the W. & P. purification process.

1. 0.1425%	4. 0.1136%
2. 0.1437%	5. 0.132 %
3. 0.1287%	Average 0.132 %

Positive results were obtained by the isonitrile test.

Experiment 10. Four samples of the drug were macerated over night with stronger ammonia water and extracted with the W. & P. solvent in a Soxhlet apparatus. The extract was purified and made up to 100 cc. 50-cc. portions of each lot were assayed.

1. 0.1352%	3. 0.1274%
2. 0.1465%	4. 0.135 %

Positive results were obtained by the isonitrile test.

The residues of the other 50-cc. portions were treated as follows:

(A) They were dried at 40° C. in a current of dry air before the addition of the standard acid;

(B) They were dried at 60° C. in a current of dry air before the addition of the standard acid.

	(A.)	(B.)
1.	0.0901%	3. 0.0665%
2.	0.0836%	4. 0.0557%

Experiment 11. Four samples of drug were macerated over night with stronger ammonia water and extracted with the W. & P. solvents in a Soxhlet apparatus. The extractive was purified, made basic with ammonia water extracted with chloroform and evaporated to dryness on a

water-bath and the residue taken up with chloroform and again evaporated to dryness. This process was again repeated, then taken up in chloroform, standard acid added and the assay completed.

1. 0.0869%	3. 0.107 %
2. 0.0871%	4. 0.0985%
	Average 0.095 %

Positive results were obtained by the isonitrile test.

Experiment 12. Samples of the drug were assayed according to the above experiment, and the final chloroform extract was dried in an oven at 80° C. for 15 minutes.

1. 0.0676%
2. 0.0893%
3. 0.072 %

Positive isonitrile tests were obtained.

Experiment 13. Three lots of drug were macerated for 1 hour with stronger ammonia water and ether, and then extracted in a Soxhlet apparatus, ether being used as a solvent.

The marc from these assays was extracted with alcohol after the addition of small amounts of stronger ammonia water. An additional amount of basic material was obtained.

First Extraction.	Marc Extract with Alcohol.	Total.
1. 0.0894%	0.0382%	0.1276%
2. 0.096 %	0.047 %	0.143 %
3. 0.094 %	0.039 %	0.133 %

Positive isonitrile tests were obtained.

Experiment 14. Eight samples of drug were macerated over night with ether and stronger ammonia water and extracted in a Soxhlet, ether being used as a solvent.

1. 0.077 %	5. 0.089 %
2. 0.0788%	6. 0.089 %
3. 0.067 %	7. 0.096 %
4. 0.072 %	8. 0.0773%
	Average 0.0812%

Positive isonitrile tests were obtained.

Aliquot portions of the last five samples obtained after the purification process were evaporated to dryness on a water-bath and dried 1 hour. The residues were taken up in chloroform, standard acid added, and the chloroform then removed by evaporation before the assay was completed.

4. 0.0413%	7. 0.039 %
5. 0.044 %	8. 0.036 %
6. 0.039 %	Average 0.0398%

These titrated residues gave no isonitrile test.

(To be continued.)

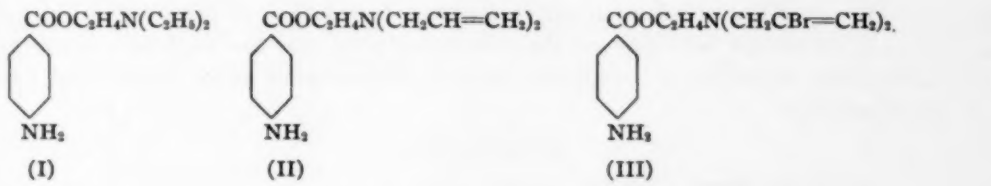
DI-β-BROMALLYLAMINO ETHYL *p*-AMINO BENZOATE.*

BY W. BRAKER AND W. G. CHRISTIANSEN.

During the course of an investigation of a variety of local anesthetics, we have prepared di-β-bromallylamino ethyl *p*-amino benzoate. This substance is analogous to procaine; the diethylamino group in the latter has been replaced

* Scientific Section, A. PH. A., Madison meeting, 1933.

with a dibromallyl amino group. The corresponding diallylamino compound is known (1). The structural relationship between procaine (I), di-β-allylamino ethyl *p*-amino benzoate (II) and di-β-bromallylamino ethyl *p*-amino benzoate (III) is indicated below.



(I) (II) (III)

The compound (III) was obtained by condensing di-β-bromallylamino ethanol with *p*-amino benzoyl chloride. The substance was isolated as its dihydrochloride. A stable 2% aqueous solution of di-β-bromallylamino ethyl *p*-amino benzoate dihydrochloride could be made, but an electrometric titration indicated the p_H of this solution to be 1.9. An effort to buffer with disodium hydrogen phosphate was unsuccessful because of the fact that the addition of a minute quantity of the buffer resulted in the precipitation of the compound.

A borate of the base (III) was also prepared but the compound was hydrolyzed in aqueous solution thereby precluding biological testing.

EXPERIMENTAL.

Preparation of di-β-Bromallylamino Ethanol.—Fifty Gm. of 2,3-dibrom propene and 8 Gm. of mono-ethanol amine were dissolved in 100 cc. of 95% alcohol; 80 Gm. of silver oxide were added in small quantities with stirring; the mixture was stirred for two hours after the addition of all the silver oxide. The mixture was then filtered and the filtrate fractionated. Twenty-five Gm. of a light yellow oil were obtained boiling at 141–145° C. at 9–10 mm. Yield—66%.

Assay.	Nitrogen.	Bromine.
Found	4.58%	53.24%
Calc. for $C_8H_{13}Br_2NO$	4.68%	53.51%

Preparation of p-Amino Benzoyl Chloride.—This was obtained by the method of McMaster (2).

Preparation of di-β-Bromallylamino Ethyl p-Amino Benzoate.—2.65 Gm. of *p*-amino benzoyl chloride were dissolved in 20 cc. of dry benzene. To this solution, one consisting of 5.1 Gm. of di-β-bromallylamino ethanol in 60 cc. of benzene was added. The solution was refluxed for 3 hours. A yellow solid which separated during refluxing was filtered off, washed with ether and dried *in vacuo*. An assay indicated that it was not the compound intended and it was not further investigated.

The benzene filtrate from the reaction was treated with dry hydrochloric acid gas. A light yellow, very viscous oil separated. The benzene layer was decanted and the oil was dried *in vacuo* over calcium chloride and sodium hydroxide.

The substance was identified by assay to be the dihydrochloride of di-β-bromallylamino ethyl *p*-amino benzoate.

Assay.	Nitrogen.	Chlorine.
Found	5.61%	15.05%
Calc. for $C_{13}H_{20}O_2N_2Cl_2Br_2$	5.70%	14.46%

SUMMARY.

(1) Di-β-bromallylamino ethyl *p*-amino benzoate was prepared.

(2) Aqueous solutions of the dihydrochloride are too acid for anesthetic tests. The solutions are incapable of buffering without precipitating the base from solution.

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(1) U. S. Patent 1,388,573.

(2) *J. A. C. S.*, 50 (1928), 145.

RESEARCH DEPARTMENT OF THE CHEMICAL AND PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB AND SONS, BROOKLYN, N. Y.

PHYSICS IN PHARMACY.

BY JOHN URI LLOYD, WOLFGANG OSTWALD AND HANS ERBRING.

(*Continued from page 221, March issue.*)

In *Fig. 13*, for example, quantities of absorbed, saturated solutions of KCl, $BaCl_2$ and $FeCl_3$, under identical experimental conditions, are recorded. With increase in valence, there is increase of absorption. Furthermore, $FeCl_3$ in dilute solution is strongly hydrolyzed. The retained liquid volume must vary, not only with the concentration of the solutions, but also with the electrocapillary effects of the different ions,[1] and finally, with the influence of the dissolved substance on the state of swelling of the cellulose fibres.

10. Influence of Concentration and Temperature.

TABLE IX.—INFLUENCE OF CONCENTRATION.

System: $FeCl_3$, concentrations *as below*, *vs.* Water. d = 1.5 mm. Paper dry at start.

Duration, Hours.	$FeCl_3$—Increase, Mm.	H_2O—Decrease, Mm.	Total Difference, Mm.
45% $FeCl_3$ Solution.			
2	0.5	1.0	1.5
5	1.0	2.5	3.5
20	2.0	4.0	6.0
40	2.6	5.0	7.6
72	3.0	6.5	9.5
23% $FeCl_3$ Solution.			
2	...	0.9	0.9
4	0.5	2.0	2.5
20	1.2	3.0	4.2
40	2.0	4.0	6.0
70	2.2	4.0	6.2

[1] We mention here the phenomena of the so-called "abnormal osmosis," cf. a résumé by K. Söllner, *Zschr. f. Elektrochemie*, 36 (1930), 234.

12% $FeCl_3$ Solution.			
10	0.2	1.5	1.7
20	0.5	2.2	2.7
40	0.6	2.5	3.1
60	0.7	3.0	3.7
70	1.0	3.2	4.2

TABLE X.—INFLUENCE OF CONCENTRATION.

System: Urea Solutions *vs.* Water; d = 12 cm. Paper dry at start.

Duration, Hours.	Urea—Increase, Mm.	H_2O—Decrease, Mm.	Total Difference, Mm.
50% Urea Solution.			
10	1.4	2.0	3.4
20	2.2	3.5	5.7
40	3.2	4.5	7.7
80	3.0	5.0	8.0
4 wks.	1.0	3.0	4.0
25% Urea Solution.			
10	0.5	0.5	1.0
20	1.0	2.0	3.0
40	1.5	2.5	4.0
80	1.5	3.5	5.0
12.5% Urea Solution.			
10	0.2	0.5	0.7
20	0.5	1.5	2.0
40	0.5	2.5	3.0
80	0.5	3.5	4.0

The influence of *Concentration* is shown in *Tables IX and X*, and in *Figs. 14* and *15* for Ferric Chloride and Urea. In the figures, the individual curves denote for the several concentrations, increases of level in cylinder S after each period of time, *e. g.*, 10, 20, 40 and 70 hours. These curves are, as it were, cross sections taken at each period of time, through the speed curves of the increase of level.

Only the sections through the ascending branch of the curves up to the maximum are here of interest.

With $FeCl_3$ (see *Fig. 14*), a group of curves is obtained, the lowermost of which, corresponding to the shortest period of time, differs very little from a straight line, while the curves obtained by sections at later periods of time have a faintly S-shaped course. It should be remembered in this connection, that $FeCl_3$, on account of its hydrolysis in solutions, represents a relatively complicated system.

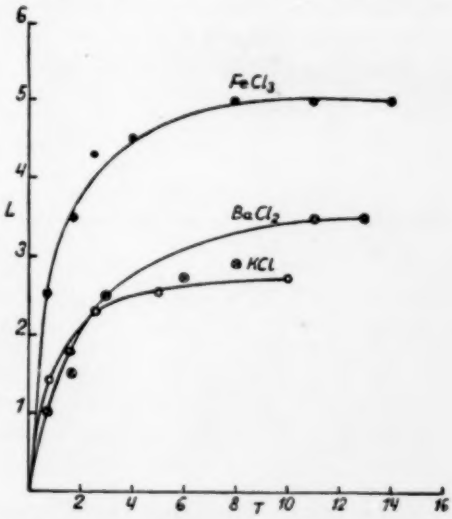

Fig. 13.—L, Quantity of liquid held back by paper, in mm.; T, Time in days.

Urea, on the contrary, shows much simpler curves, the two lowermost of which

differ but little from a straight line. All deviations, however, are in the sense of curvature *convex* to the axis of concentration. Still, this mode of deviation and curvature is characteristic for most of the concentration functions of the directly measured osmotic pressure of concentrated solutions, whether molecular-disperse or colloidal.[1]

Influence of Temperature.—To study the influence of temperature, experiments were carried out under identical conditions, except that the temperature in one case was 20° C. (room temperature), in the other 50° C. (Air-thermostat).

TABLE XI.

System: $FeCl_3$ (saturated), *vs.* Water. $d = 7$ cm. Paper dry at start.

Duration.	Increase of Level at 20°.	Increase of Level at 50°.
4 hrs.	0.8 mm.	0.9 mm.
30 hrs.	1.4 mm.	1.6 mm.
50 hrs.	2.1 mm.	2.5 mm.

Table XI shows a slightly higher increase of level at 50° than at 20°.

11. Isothermal Distillation.—We mentioned before, that part of the liquid evaporates and condenses along the walls of the tubes. This suggested the possibility that water, having a higher vapor pressure, may be transferred into cylinder S through isothermal distillation. No doubt such a process takes place; but we can show that isothermal distillation, alone, is not sufficient to produce the Effect here described.

In order to test out this possibility, experiments were conducted with identical arrangement of apparatus, except that *filter paper was not used*. If in the course of time differences of level develop under these conditions, they can be explained only through differences of vapor pressure. Our experiments (see *Table XII*) have shown that after about 3 days, a small difference of level in the expected direction, indeed, appears. This difference, however, is incomparably smaller than the experiments with filter paper have shown, in which, in a shorter time, a value 20 times as much has often been obtained.

TABLE XII.

System: $FeCl_3$ (saturated), *vs.* Water.

Duration.	$FeCl_3$ Increase.	H_2O Decrease.	Total Difference.	Length of *d*.
2 hrs.	...	...	...	4 cm.
20 hrs.	...	...	...	
72 hrs.	0.3 mm.	1.0 mm.	1.3 mm.	
5 days	0.5 mm.	1.5 mm.	2.0 mm.	
20 hrs.	0.2 mm.	0.2 mm.	0.4 mm.	1.5
48 hrs.	0.7 mm.	0.7 mm.	1.4 mm.	
60 hrs.	0.7 mm.	0.7 mm.	1.4 mm.	
5 days	1.0 mm.	1.0 mm.	2.0 mm.	

These results show that the differences in vapor pressure produce our Effect on a very small scale, hence the velocity of isothermal distillation is far too small to account for the relative magnitude of our Effect.

[1] Cf. Wo. Ostwald, *Kolloid-Z.*, 49 (1929), 62, 80; 56 (1931), 263; *Z. physiol. Chem.-A*, 159 (1932), 375.

Surface Tension.—Motions in capillary systems have been linked with differences in surface tension since Dutrochet, and more recently, since I. Traube and others. The capillary rise in filter paper is of course a result of surface tension, and will vary in height or speed, according to the magnitude of the tensions of the two liquids. As soon as the 2 liquids have met in the filter paper, however, there can no longer be any difference of surface tension between them. There may remain differences in *wetting power*, which would lead to the displacement of the pure solvent by the better wetting solution. Thus a movement of liquids might arise which, however, would stop at once when the capillaries of the filter paper are saturated with the better wetting, dissolved substance.

In order to examine the extreme case of such a wetting current, a very dilute (0.05%) soap solution was placed against pure water. In this case, the difference of the two surface tensions is extremely great, at any rate considerably greater than, *e. g.*, in the case of $FeCl_3$ *vs.* water. Also, the wetting power of soap solution is naturally greater than that of pure water. The effect produced is shown in *Table XIII.*

TABLE XIII.

System: Sodium Palmitate (0.05%) *vs.* Water.

Duration.	Soap Solution, Decrease.	Water, Increase.
24 hrs.	1.0 mm.	...
46 hrs.	1.0 mm.	...
70 hrs.	1.5 mm.	1.0 mm.
8 days	1.5 mm.	1.0 mm.
10 days	1.5 mm.	1.2 mm.
15 days	1.5 mm.	1.2 mm.

A transfer of soap solution to water is distinctly noted; but again the Effect is of considerably smaller magnitude than in the case of $FeCl_3$ *vs.* H_2O, notwithstanding the fact that the difference in surface tensions and wetting powers is much greater in the former than in the latter. Besides, the movement ceases after about 3 days, which agrees with theoretical prediction.

Thus the source of energy causing the Effect described, cannot reside in differences of surface tension and of wetting power.

III. THEORY OF THE EFFECT.

Before giving the theoretical explanation of the Effect, we will summarize once more the principal phenomena graphically, as it is done in *Fig. 16.* The Effect, as to time, takes place in three parts (I, II, III). To these, strictly speaking, should be added a "prelude," consisting in the preliminary capillary rise of both liquids.

In *Fig. 16, A* shows the rise in the salt tube, or the difference of level of both liquids during the experiment. *D* shows the location, resp., the migration of the diffusion zone between salt solution and water during the process. This migration within the filter paper is represented somewhat more plainly in *C.* Finally, *D* shows the change of the average difference of densities of the liquids to the right and the left of the filter paper during the process. This difference of density is only estimated from the intensity of coloration, *e. g.*, in the experiments with $FeCl_3$; hence the curve cannot be considered of quantitative value, although it correctly represents differences of actual observation.

With the aid of this synoptical *Fig. 16*, we present the following:

THEORY OF THE EFFECT.

Preliminary Process: Water as well as salt solution, rises in the siphon as a result of surface tension.[1] The liquids meet in the filter paper.

In our experiments, the salt solution was given an advantage in order to enable the two liquids to meet at about the middle of the strip (cf. *Fig. 16, C–I*). This is

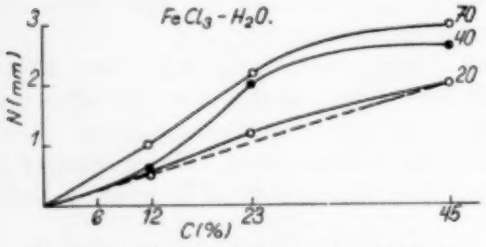

Fig. 14.—C, Concentration in %; N, Increase of level in mm.; Concentration curves after 20, 40 and 70 hrs.

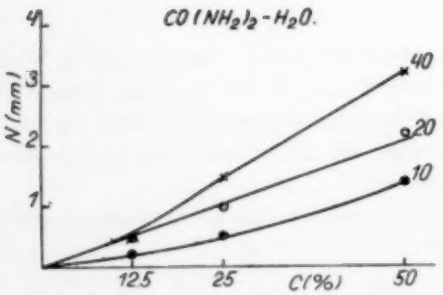

Fig. 15.—C, Concentration in %; N., Increase of level in mm.; Concentration curves after 10, 20 and 40 hrs.

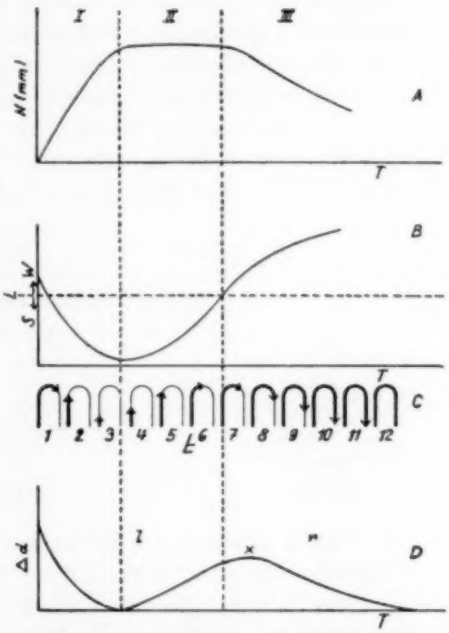

Fig. 16.—Scheme A: N, Rise in the salt tube, or difference of level of both liquids; T, Time. Scheme B: L, Position of zone limit of diffusion; W, Water tube; S, Salt tube; T, Time. Scheme C: L, Position of zone limits of diffusion. Scheme D: Δd, Average difference of densities of liquids to left and right in filter paper; l, Left tube heavier; r, Right tube heavier; T, Time.

the starting condition, at which, in our experience, the Effect manifests itself most strongly.

I. The *First Divisional Effect* consists in a steep rise of liquid in the salt tube, *i. e.*, a sharp increase in the difference of level, with which is connected a sinking of the interface salt-solution-water in the salt tube (easily recognized with colored salts), and finally a corresponding decrease of the differences of weights of the liquid cylinders in both siphon tubes (cf. *Fig. 16, I–D*).

[1] The remarkable phenomena of capillary rise of solutions in filter paper have been pointed out by the senior author, more than 50 years ago. PROC. A. PH. A., 1879–1885; reprinted in *Kolloidchem. Beihefte*, 8 (1916), 174.

At least three sources of energy may be named as bringing about this movement of liquids. First, the process is evidently that of a hydrostatic siphon effect. When we connect two liquids of different densities by means of a siphon, as depicted in *Fig. 17*, hydrostatic equilibrium will exist only when the products of height times density are equal in both arms of the siphon. In the arrangement shown in *Fig. 17a* (adopted in our experiment), the weights of the liquid columns in both branches are evidently not equal at the start. Therefore, liquid will move in the direction of the arrow, from water to salt solution, which continues until the two liquid columns, now of different lengths, have again attained equal weights (cf. *Fig. 17b*). In contrast with an ordinary siphon with large cross section (*e. g.*, a glass tube), the hydrostatic equilibrium in our experiment does not take place instantaneously, but requires, for example, up to about 10 days' time. This is not

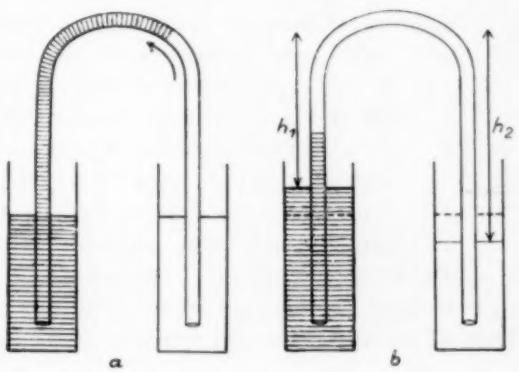

Fig. 17*a*. Fig. 17*b*.

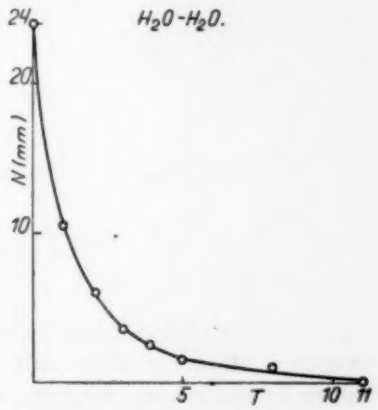

Fig. 18.—N, Difference of level in mm.; T, Time in days.

surprising when we consider the fact that, according to Hagen-Poiseuille's law, the velocity of flow decreases exceedingly fast with the diameter of the capillary tubes; for circular pipes in the ratio of r^4, *i. e.*, the fourth power of the radius. Besides, we have in filter paper very irregular capillary spaces, which compel the current to follow detours.

The slowness of a purely hydrostatic equalization in filter paper is well illustrated by the experiment of *Fig. 18*. Hydrostatic equalization was observed in a system containing water on both sides, but in which a difference of level of 24 mm. was given to it at the start. About 11 days were required for the termination of this purely hydrostatic equalization.

Thus, one explanation of the 1st divisional effect which readily suggests itself, would consider the rise as a simple hydrostatic *Capillary Siphon Effect*.

However, this explanation does not exhaustively describe the dynamics of the process. Another source of energy exists, for it is evident that within a period of 11 days of experimentation, with the system employed, *Diffusion* must also become effective. In the capillary siphon we have a continuous passage between salt solution and water, which presents the preliminary conditions for diffusion to manifest itself. The diffusion of the salt molecules takes place in opposite direction to that

of the water current, which from hydrostatic causes, flows from the water tube to the salt tube. Although this current overcomes the motion of diffusion, as is evidenced by the retrogression of the joint diffusion surface, diffusion will nevertheless not be completely inactive. It will rather act always in the direction of increasing the weight in the salt tube, *i. e.*, constantly supporting the hydrostatic effect. Hence, the mechanism of liquid movements during the first divisional effect, is a combination of a purely hydrostatic effect (represented by the initial condition), and a simultaneous secondary hydrostatic effect produced by diffusion. Thus the strip of paper acts at first as a "capillary siphon," as well as a *Diffusion Siphon.*

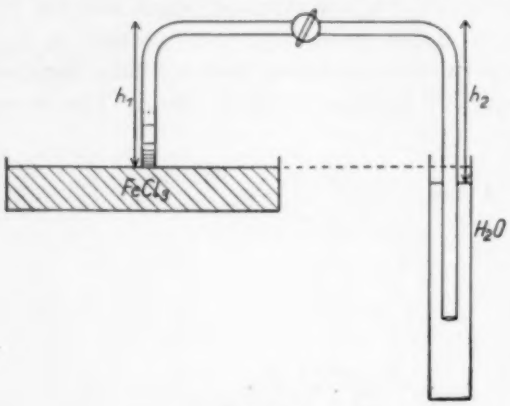

Fig. 19.

The mode of action of such a "Diffusion Siphon," can very well be demonstrated by the following arrangement of apparatus, to which E. Manegold—Göttingen kindly called our attention.[1] *Fig. 19.* A bent capillary tube dips at the left end directly beneath the surface of a salt solution contained in a wide dish, at the right into water contained in a narrow cylindrical glass vessel. The siphon, fitted with a glass stop-cock in its center, is first filled with water. On opening the stop-cock, diffusion of the salt begins, evidenced by the drawing up of water, as shown by the following figures, for which we are also under obligation to E. Manegold:

Time:	3 days	5 d.	7 d.	9 d.	10 d.
Differences of level:	2.1 mm.	3.5 mm.	4.9 mm.	5.59 mm.	6.7 mm.

However, the effect of diffusion very probably is not only hydrostatic; this brings us to the consideration of a *third* source of energy for the first divisional effect.

It is generally accepted that a dissolved substance, also a diffusing substance, develops an *osmotic pressure.* This osmotic pressure becomes hydrostatically active and measurable, only when the solution meets a mechanical obstacle which hinders the mobility of the dissolved molecules, but not the mobility of the solvent. It is merely another expression of the same fact when we substitute for the term "osmotic pressure," the osmotic attraction of the solvent by the dissolved particles. Ordinarily, the scheme of a semipermeable membrane is selected in demonstrating this tendency of the solvent being attracted by the dissolved molecules; this effect is explained in molecular kinetics by a bombardment of the membrane by the dissolved molecules. It seems, however, that the scheme of a semipermeable membrane is not the only possible method of converting the osmotic pressure into a hydrostatic one, demonstrating the osmotic attraction of liquids. According to the customary

[1] We sincerely thank Dr. Manegold for this friendly suggestion, as well as for others, kindly made.

notion, the dissolved molecules bounce perpendicularly upon the membrane. When the membranes are thick and curved cylindrically, a *slanting*, or even *tangential* impingement of the molecules upon the cylindrical walls of the pores is possible, and has already been the subject of discussion. Also, the well-known experiments of Bartell and Bigelow,[1] E. Cohen[2] and others, have shown that osmotic effects may be observed, also, in clay cylinders, whose pore-diameters are notably greater than the diameter of the dissolved molecules (osmotic pressure with permeable membranes).[3]

In pursuing these reflections, we may conclude that in the case of diffusion in a capillary system of the nature of filter paper, the conditions are realized for the manifestation of osmotic effects, *i. e.*, an attraction of the solvent by the salt molecules, here also hindered in their mobility. In such a system, the salt molecules will strike with exceedingly great frequency against the side walls, will thereby suffer a retardation of motion, and thus attract solvent in the same manner as they do in an ordinary osmotic cell. Then we should be dealing here with "Osmosis without membrane," or "Capillary Osmosis." Even in the case when the origin of osmotic pressure is not referred to molecular kinetics, but if, *e. g.*, as H. Hulshof[4] has done, a "tangential pressure" and an activity of the capillary layer are introduced, based on thermodynamic points of view, a capillary system of the character of filter paper may also be placed in parallel with the usual membrane.

This third explanation of the "first divisional effect" would then be formulated as follows: The impinging of the salt molecules upon the capillary walls of the strip of filter paper causes retardation of the free movement, and consequently of the diffusion of the salt molecules, but not of the movement of the water molecules, which are present in excess. Therefore, an osmotic pressure arises in the direction toward the salt molecules, thus an attraction of the solvent. This osmotic attraction of the solvent would act in the same sense as the two first-named sources of energy, at least as long as there is salt in the lower part of the salt tube. If the salt diffuses further upward, the scene of its osmotic activity would also move upward. We shall shortly discuss this effect more in detail.

To sum up: There are three sources of energy for the "first divisional effect:" (1), A primary hydrostatic pressure, existing at the start of the system; (2), A secondary hydrostatic pressure, caused by diffusion and corresponding increase of weight in the salt tube; (3), Capillary-osmotic pressure, likewise caused by the diffusing salt molecules.

(End of Second Instalment.)

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[1] F. E. Bartell, *J. Phys. Chem.*, 16 (1912), 318; Lawrence Bigelow and F. E. Bartell, *J. Am. Chem. Soc.*, 37 (1909), 1194.

[2] E. Cohen, *Z. physik. Chem.*, 64 (1908), 1.

[3] Cf. also the detailed discussions by E. Manegold and Solf, *Kolloid-Z.*, 59 (1932), 179; further literature there given.

[4] H. Hulshof, *Z. physik. Chem.*, 128 (1927), 110; *Proc. Acad. Amsterdam*, 33 (1930), No. 2.

Dedication of the American Institute of Pharmacy at Headquarters Building, Wednesday, May 9th, at 10:00 A.M.

AN EXAMINATION OF CEANOTHUS VELUTINUS.*

BY L. W. RICHARDS AND E. V. LYNN.

This member of the buckthorn family is an evergreen shrub found from British Columbia to California and from the Rocky Mountains to the Pacific Coast. It is commonly known as sticky laurel or as mountain balm, but also by other names. It grows best in sandy or rocky soil in the hills and is found profusely on logged-off land, of which the acreage on the coast is large and constantly increasing. Wahlenberg (5) has recommended it as an aid in reforestation.

The leaves are covered with a sticky substance of cinnamon-like odor, which the flowers also possess in a magnified degree. Because of this waxy matter the plant is considered a serious fire-menace in the Californian forests.

The plant has previously been examined three times, but not exhaustively. In 1916, Scalione and Blakemore (2) made an investigation, particularly of the wax, 7.3 per cent, and of the tannin, 17.3 per cent. In 1922, Howard (3) classified the leaf-wax as a balsam because it yielded a volatile oil and cinnamic acid. A year later Lynn, Lee and Clausen (4) distilled an oil from the leaves and suggested that it is largely aldehyde.

The eastern species, *Ceanothus americanus*, has been examined extensively and repeatedly since the middle of the last century. An alkaloidal mixture, ceanothyn, is well known in certain medical circles; it is obtained from the roots and root-bark.

The material used in this work was gathered mostly near Seattle, but also partly near Missoula, Montana. It was freed from foreign matter, cleaned well and dried in the air. Some of the roots and leaves were powdered before use.

Histological.—In order to throw some light on the origin of the sticky coating, which is found in great abundance on the leaves, permanent and temporary sections of the latter were made. These revealed at frequent points pear-shaped structures descending from the upper epidermal cells, the point near the surface consisting of two parallel rows of large, pentagonal cells. The two rows separated half way down and formed the circular end. Within this cavity was found a network of smaller, thick-walled cells which undoubtedly is conductive tissue and forms a canal through the leaf. Of course, the stomates are on the under side of the leaf, not on the upper surface. While the interior portion of this peculiar structure was easily stained by various reagents, the large outer cells were unaffected by any of them. Although the content would suggest a secretory layer, there is no reason to relate the structure to secretion. Dr. Eames, of Cornell, expressed the opinion that the cylinders are bundle-sheaths and probably not linked with the balsam, and in this Dr. Rigg of Seattle concurs. It is interesting to note, however, that the structure is not possessed by any of six other species of *Ceanothus*, which also do not have the balsamic coating. These are *prostratus*, *americanus*, *ovatus*, *pubescens*, *fendleri* and *thyrsiflorus*. The structure was found to be missing in the leaf-bud and in very immature leaves. It evidently appears at the time when the tissues are first differentiated according to function.

Proximate Analysis.—This was made in the usual way on the leaves and on the root-bark.

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	Leaves.	Root-Bark.
Loss in air	50.6	48.3
Ash	4.5	6.5
Petroleum-ether extract	12.8	0.5
Ether extract	12.8	2.2
Crude fibre	12.3	17.6
Total nitrogen × 6.25	10.6	..

Selective Extraction.—The bark, wood and flowers were each submitted to selective extraction by the solvents given. The results follow:

	Bark.	Wood.	Flowers.
Petroleum ether	1.18	0.75	2.84
Ether	1.89	0.27	2.48
Alcohol	12.40	4.51	13.85
Acetone	0.42	0.59	3.47
Carbon disulphide	0.04	0.14	None
Ethyl acetate	0.07	0.04	None
Water	8.36	3.72	16.70

Volatile Oil.—The flowers furnished 0.1 per cent of an oil which was apparently unlike that from other parts of the plant. The total amount of flowers available was not sufficient to warrant any examination of the oil.

From the leaves by distillation with steam, there was obtained 0.14 to 0.21 per cent of oil, the amount being largest during the winter months and gradually decreasing up to the time of flowering in May and June. Judging by the index of refraction, however, the oil obtained at different times of the year was constant in composition. It was reddish brown in color and possessed a strong, aromatic and pungent odor. The constants were: specific gravity at 20° C. 0.9565; index of refraction at 20° C. 1.509 to 1.542; specific rotation −12.5°; saponification number 148.4, 142.0 and 155.0; 22 per cent soluble in sodium hydroxide; 20 per cent soluble in sodium bisulphite solution.

The whole oil was fractionated and refractionated several times at 5-mm. pressure with final results as given in the table:

Fraction, Degree.	Per Cent.	Approximately at 760 Mm., Degree.	n at 20° C.
65– 80	7.5	165	....
80– 90	8.0	190	1.5360
90– 94	14.0	211	1.5600
94– 98	7.5	214	1.5691
98–120	4.5	230	1.5031
120–125	4.0	239	1.4859
125–128	4.5	252	1.5015
128–135	3.0	259	1.5110
135–145	5.0	266	1.5150
145–157	9.5	273	1.5180
157–165	7.0	280	1.5200
Residue	25.5	...	....

The chief constituents were found to be ethyl and cinnamyl cinnamates, the former in fractions 8–10 and the latter in these and the residue. Saponification of the oil boiling at 132–135° gave cinnamic acid, melting at 132° C. and

oxidizing with potassium permanganate to benzaldehyde. The separated aqueous solution contained ethyl alcohol which was isolated and identified by conversion to the benzoate and acetate. Cinnamyl cinnamate, melting point 43–44° C., was separated by treatment with warm alcohol and was further characterized by saponification to cinnamic acid and cinnamyl alcohol, whose phenyl urethane melted at 90° C.

Salicylaldehyde, semicarbazone melting at 225° C., was apparently the chief component of fractions 2 and 3, which gave with ferric chloride a deep violet color.

The fraction boiling at 126–128° probably contained esters of an alcohol with a strong odor like geraniol, although a diphenylurethane melting at 56° C. and a phthalate melting at 204–205° C. could not be referred to a known alcohol. The acids from saponification were cinnamic acid and probably valeric acid, the latter partly identified by odor and boiling point.

The lowest fraction contained terpenes which were not identified. From Fraction 2 a bromide was separated with a melting point of 105° C. (limonene?) and from Fraction 4 a bromide melting at 124° C. (dipentene?). Fraction 10 also furnished a bromide melting at 92° C. No further study was made of these. The residue contained, with the cinnamyl cinnamate, a paraffin melting at 62° C.

It is interesting to note that cinnamic aldehyde could not be identified in any of the fractions, notwithstanding that the odor is suggestive and that others have predicted its presence.

Alkaloid.—Preliminary experiments proved that the leaves do not yield alkaloids, but that some could be extracted from the bark and more from the root-bark. For further study a large quantity of the latter was collected, dried and ground to a coarse powder. After considerable experimentation, it was found best to extract first with chloroform, from which the alkaloidal material was removed by means of very dilute sulphuric acid. This solution gave with ammonia a copious, curdy, white precipitate which could again be collected by chloroform. After repetition of the process several times, the precipitate was collected and dried, the yield being approximately 0.1 per cent.

It was very soluble in chloroform and fairly so in hot alcohol or hot methyl alcohol, but was only slightly soluble in the cold alcohols, in ether, acetone, petroleum ether, benzene or carbon tetrachloride. It was practically insoluble in water. By means of hot methyl alcohol, there were obtained minute crystals in the form of raphides or needles, which were perfectly colorless. This crystalline material decomposed when heated slowly and melted at indefinite points; when the temperature was raised quickly, the melting point was fairly constant at about 270° C. with decomposition.

Analysis by combustion gave figures which agreed closely with the simple formula, $C_{23}H_{26}N_2O_4$. Those for six consecutive determinations of carbon and hydrogen and three for nitrogen were as follows:

	1.	2.	3.	4.	5.	6.
Carbon	69.7	70.0	69.9	69.8	70.2	70.0
Hydrogen	7.0	7.0	7.1	6.8	7.0	7.2
Nitrogen	7.2	7.3	7.3	....	....	....

Calculated for $C_{23}H_{26}N_2O_4$: Carbon 70.0, hydrogen 6.5, nitrogen 7.1.

To determine the molecular weight by the freezing-point method was impracticable

because of insolubility in the proper liquids. The boiling-point method also proved unsatisfactory, because the small amount of material precluded using a suitable apparatus like those of McCoy or Cotrell. The figure obtained in one experiment was 125, calculated 394.

Precipitating agents, except tannic acid, gave very satisfactory reactions with acidified aqueous solutions.

Reagent.	Precipitate.
Mayer	Very small white granules
Sonnenschein	Amorphous, light blue
Scheibler	Amorphous, white
Wagner	Amorphous, brown
Wormley	Amorphous, yellow
Picric acid	Granular crystals
Platinum chloride	Small, light yellow, granular crystals
Cold chloride	Amorphous, yellow
Hydrobromic acid	Amorphous, white
Hydriodic acid	Amorphous, brown

A few color reactions were noted, although no attempt was made to study these completely. Froehde s reagent gave a green color changing to brown and then back to green. Marquis' reagent yielded a green turning slowly to a brown. Mandelin's reagent produced a yellow color which later became brown. No reactions were obtained in the Vitali test, with concentrated ammonia water or in the fading purple test as for strychnine. Nitric acid gave a blue-green color which soon changed to purple and finally faded. Sulphuric acid produced a yellowish brown and finally a purple. Hydrochloric acid gave a beautiful blue which later became green.

The hydrochloride was prepared, by passing dry hydrogen chloride into a chloroformic solution, as a white, agglutinated mass which was very unstable and gave no definite melting point. It was completely decomposed at 240° C. Analysis by the usual methods gave 5.4 and 5.8 per cent of chlorine, compared to 8.2 per cent is calculated for a monchydrochloride.

The small amount of material available prevented any further study, but plans are now being laid to collect larger quantities of root-bark and to examine the alkaloid more carefully, chemically and pharmacologically.

Coloring Matter.—Extracts of leaves, bark and root-bark contained coloring agents which did not respond to the Bornträger test, in spite of the fact that many of the Rhamnaceæ contain anthraquinone derivatives. Aqueous or alcoholic extracts of the root-bark were of a bright red color, from which ammonia precipitated a gelatinous, purple substance. This was soluble in acid to give a red solution, but was not soluble in any of the organic liquids. Qualitatively it gave several reactions which are characteristic of anthraquinone derivatives and we plan to study it further.

Dermatitis.—In 1905, Rooney (1) described somewhat a dermatitis which was attributed to *Ceanothus velutinus*, and a number of persons in Washington have orally reported similar experiences. In view of the wide-spread occurrence of this plant, it is very possible that many cases of poisoning laid to species of *Rhus* are in reality caused by *Ceanothus*. With the aid of Drs. Wm. Clausen and Henry Odland, both dermatologists, it was found that such a dermatitis could be caused

on a small percentage of subjects by either the leaves or an ethereal extract of them, but that aqueous solutions are inactive. One of the writers was continually affected during collection of material.

The eruption appeared on the skin one or two days after contact. The first symptoms were itching and burning, with subsequent redness, and finally vesicles appeared on the surface. On the face the skin became bright red and the eyelids and surrounding tissues were markedly swollen. These symptoms continued for two or three weeks after exposure and then gradually subsided. Simultaneously, desquamation occurred in the form of small scales and large flakes of dried epidermis. Treatment by the antigens of poison oak or ivy was of no prophylactic or curative value, but the conditions were relieved by the usual moist compresses and soothing lotions.

SUMMARY.

The leaves of *Ceanothus velutinus* present microscopically a peculiar structure which is not found in other species and may be related to the characteristic balsamic coating. They furnish 0.14 to 0.21 per cent of an oil which is chiefly ethyl and cinnamyl cinnamates, with smaller amounts of salicylaldehyde, terpenes and esters of an unidentified alcohol with cinnamic and probably valeric acids. The root-bark furnishes about 0.1 per cent of alkaloid, part of which was obtained in the crystalline state. Analysis indicated the formula $C_{23}H_{26}N_2O_4$. Some study was made of its properties and reactions. Reports of a dermatitis from the leaves were confirmed and the symptoms are described.

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October 1, 1932.

THE INTERNATIONAL STANDARD FOR THE ŒSTRUS-PRODUCING HORMONE.

At the request of the officers of the Permanent Commission on Biological Standards of the Health Organizations of the League of Nations, the Board of Trustees of the U. S. Pharmacopœial Convention has agreed to assume the responsibility for distributing the International Standard for the Œstrus-Producing Hormone in the United States. Supplies of this material have just been received from the National Institute for Medical Research, London, where the International Standard has been prepared. This Standard is now available for the use of manufacturers of preparations of this Hormone, for the purpose of establishing for their products a uniform potency in the terms of the International Unit; one International unit consists of 0.0001 mg. of the Hormone issued by the League of Nations. This material is also available for those carrying out important therapeutic researches in this field.

A memorandum suggesting the course to be followed in using the International Standard, has also been supplied by Dr. H. H. Dale, Director of the National Institute for Medical Research. Those who are interested in securing this memorandum or the International Standard, should communicate directly with E. Fullerton Cook, Chairman of the U. S. P. Committee of Revision, 43rd Street and Woodland Avenue, Philadelphia.

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COMPARISON OF KARAYA GUM AND TRAGACANTH.*

L. F. GABEL.

Karaya Gum (*Sterculia urens*) was formerly known as Indian Gum. It comes chiefly from India. The use of Karaya Gum in the preparation of toilet articles has increased in recent years. This has been due to the discovery that Karaya possesses certain physical properties that make it superior to Tragacanth for some purposes.

This laboratory has obtained data in regard to the comparative value of mucilages of Karaya and Tragacanth, and as the literature lacks information on this point, considered it worth while to publish the results.

I. KARAYA GUM DIFFERS FROM TRAGACANTH IN PHYSICAL AND CHEMICAL PROPERTIES AS SHOWN IN THE FOLLOWING TABLE.

TABLE I.

	Karaya.	Tragacanth.
Physical form	Lumps	Ribbons
Chief chemical principal	Gelose	Bassorin
Solubility in water	More soluble than Tragacanth	
Reaction	Acid (1 Gm. requires 4.5 cc. *N*/10 alkali to neutralize)	Acid (1 Gm. requires 0.9 cc. *N*/10 alkali to neutralize)
Appearance of solution in water	Translucent	Opalescent
50% Alcohol	Clear	Precipitates
Borax test (U. S. P.)	Stringy and slimy	Not affected
Iodine T.S.	Colorless—free from starch	Blue color—starch present
Density	1.20	1.25

II. MUCILAGE OF KARAYA GUM COMPARED WITH MUCILAGE OF TRAGACANTH.

Mucilages of the gums were prepared according to the following formula:

Powdered gum	42 grains
Glycerin (used as preservative)	5 oz. av.
Sufficient water to make	8 oz. av.

Tests were applied to the mucilages to note:

1st Ability of the gum to form thick mucilage.
2nd Effect of aging on the mucilage.
3rd Differences in viscosity due to the method of manufacture, *i. e.*, 1st set of experiments prepared with heat, 2nd set prepared by heating to boiling, 3rd set prepared by boiling two minutes, 4th set prepared by boiling five minutes, 5th set prepared by boiling ten minutes.

* Section on Practical Pharmacy and Dispensing, A. PH. A., Madison meeting, 1933.

In all experiments in which heat was used, the lot was allowed to cool and then sufficient water added to make 8 oz. av. of mucilage.

The MacMichael Viscosimeter was used to note the variations in viscosity. Readings were obtained with the following standards:

Disc plunger
No. 22 wire
Room temperature
8 r. p. m.

The disc plunger is held or supported in contact with the mucilage by a standard No. 22 wire. The container holding the mucilage rotates at 8 revolutions per minute. The resistance to the wire imparted by the viscosity of the mucilage is registered on a dial and the number of divisions indicated on the dial multiplied by 205 permits a mathematical comparison in terms of poises. However, an easier comparison can be made by recording the divisions registered on the dial, as the poises run as high as 26,000, whereas the readings on the dial are simple numbers.

TABLE II.

		Method of Manufacture.				
Gum.	Aging Period.	Made without Heat.	Brought to Boil.	Boiled Two Minutes.	Boiled Five Minutes.	Boiled Ten Minutes.
Tragacanth	Original reading	17	19	39	61	61
Aleppo	After 3 months	73	84	90	108	101
No. 1	After 10 months	93	117	140	120	115
Karaya	Original reading	14	35	20	21	25
Superior	After 3 months	26	34	27	28	26
Grade	After 10 months	20	19	15	15	10

The above table shows changes in viscosity during a ten-month aging period.

Comparison:

1st. Tragacanth produces a thicker mucilage.
2nd. Tragacanth Mucilage becomes thicker on aging; Karaya becomes thinner on aging.
3rd. A two-minute boiling period is required to obtain thickest mucilages of Tragacanth.
4th. Application of heat in the preparation of mucilage of Karaya should be avoided.

TABLE III.

			Method of Manufacture.			
Gum.	Aging Period.	Treatment.	Made without Heat.	Boiled Two Minutes.	Boiled Five Minutes.	Boiled Ten Minutes.
Tragacanth Aleppo No. 1	Original reading	W/o neutralization	91	140	130	110
		Neutralized	85	49	27	27
	After two months	W/o neutralization	128	140	138	117
		Neutralized	160	55	30	29
	After four months	W/o neutralization	145	150	150	120
		Neutralized	147	48	28	26
Karaya Superior Grade	Original reading	W/o neutralization	68	63	56	46
		Neutralized	93	...	...	...
	After two months	W/o neutralization	59	63	60	55
		Neutralized	64	69	53	44
	After four months	W/o neutralization	35	45	40	33
		Neutralized	36	27	25	21

The preceding experiments were repeated with three different samples of high grade Karaya and Tragacanth gums, and although slight variations occurred in viscosity, the general results were the same.

Karaya gum is five times as acid as Tragacanth. Because of the possibility of incompatibility due to the acid, and also to note effect of neutralization, a series of experiments was made in which one-half of each experiment was neutralized. The standard formula for the mucilage used in obtaining results for Table II was again used, with a like series neutralized with potassium hydroxide. The same standards used in obtaining data for Table II were used in Table III.

There is an interesting observation drawn from the above results, *i. e.*, neutralized mucilages of Tragacanth made with the aid of heat show a stable viscosity, though decidedly less viscous than the mucilage made without neutralization and without heat.

This establishes the fact that the acid in Tragacanth effects a decrease in mucilaginous properties when heat is applied to the powdered gum or mucilage. Heat should be avoided as much as possible in powdering gum Tragacanth.

Because neutralized Karaya mucilage becomes stringy, the results in the above table are of no consequence.

In order to present the comparison of the two mucilages in another way which is more applicable, experiments were prepared containing $^3/_4\%$, 1%, $1^1/_2\%$ and 2% of the gums, respectively. The solutions were prepared without aid of heat.

As the viscosity as determined by the viscosimeter does not definitely indicate the fluidity of a preparation, it was necessary to introduce another test to note this physical property.

The standard used to obtain the following data consisted of a glass tube 36 inches long, with a bore of 1 centimeter. The number of seconds required for a 30-inch column of mucilage to flow from the tube held in a vertical position was noted.

TABLE IV.

		% Strength of Solution of Gums. Standards—MacMichael's Viscosimeter—No. 22 Wire-Disc Plunger—8 R. P. M.—No. Divisions Revolved. Flow Test—30-Inch Column—1-Cm. Bore. No. of Seconds Required to Flow.							
		$^3/_4\%$		1%		$1^1/_2\%$		2%	
Gum.	Aging Period.	Viscosimer.	Flow Test.	Viscosimer.	Flow Test.	Viscosimer.	Flow Test.	Viscosimer.	Flow Test.
Tragacanth	Original reading	11	..	30	..	72	...	211	..
Aleppa	After 4 months	18	..	43	..	87	...	235	..
No. 1	After 6 months	20	6	47	29	94	140	236	..
Karaya	Original reading	151	..	28	..	64	...	121	..
Superior	After 4 months	8	..	21	..	35	...	91	..
Grade	After 6 months	6	..	13	1	19	3	55	23

Three samples of each gum were tested as shown in the above table and the results were similar.

The above results again show that aging increases the viscosity of Tragacanth solution and decreases the viscosity of Karaya solution.

Based on the flow test, a 1% solution of Tragacanth has approximately the fluidity of a 2% Karaya solution after aging about six months.

CONCLUSIONS.

1. Tragacanth has greater mucilaginous properties than Karaya. It is necessary to use fully twice as much Karaya to obtain a comparative thick mucilage with Tragacanth.

2. Maximum viscosity is obtained by boiling the Tragacanth mucilage two minutes; Karaya mucilage by manufacture without the aid of heat.

3. The greater acidity of Karaya should be considered in pharmaceutical preparations as a source of incompatibility.

4. Tragacanth mucilage becomes thicker on aging; Karaya mucilage becomes thinner on aging.

Karaya possesses the following advantages over Tragacanth:

1. More readily soluble. One per cent of Karaya can be completely dissolved in water in 30 minutes.

2. Karaya mucilage applied to the skin produces a softer effect than Tragacanth.

3. Karaya is preferable to Tragacanth when used in hair preparations.

Tragacanth produces a very stiff effect to the hair, whereas Karaya spreads better and keeps the hair in place without the conspicuous stiff "board" effect common to Tragacanth hair products.

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LIQUOR CALCIS SULPHURATÆ.*

BY R. A. CAIN[1] AND H. A. LANGENHAN.[2]

PRELIMINARY REPORT.

Experience in the preparation of Liquor Calcis Sulphuratæ N. F. has shown that it is almost impossible to obtain a solution of uniform strength by following the N. F. directions. Not only do the finished solutions vary in strength when prepared by different members of a class, but also when made by the same person.

The purpose of this investigation was to determine, if possible, whether or not the quantities of lime and sulphur could be reduced, and to outline a method whereby a finished product of a uniform strength could be obtained.

A total of 16 solutions was prepared, some according to the directions in the N. F. while in others the quantities of the ingredients were altered as well as the technique used in preparing the solutions.

Two solutions were made according to the N. F. directions, *i. e.*, by adding a mixture consisting of 165 Gm. of lime and 250 Gm. of sulphur to 1750 cc. of boiling water. The mixture was boiled and reduced to 1000 cc., at which volume it was maintained, while boiling, by the frequent addition of water. The mixture was allowed to cool and finally strained through muslin. The finished solutions were

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.

[1] Instructor in Pharmacy.

[2] Professor of Pharmacy.

assayed for their lime and sulphur content, the results of which are shown in the following table:

Solution No.	Cc. Collected.	% CaO.	% S.	Total CaO Gm.	Total S Gm.	% CaO Used.	% S Used.
1	540.0	16.42	25.9	88.66	139.86	53.73	53.94
2	590.0	10.94	22.3	64.54	131.57	39.11	52.62
Av.	565.0	13.68	24.1	76.60	135.71	46.42	54.28

It will be noted that although both solutions were prepared in a similar manner, the amount of finished product finally collected was 50 cc. greater in solution No. 2. Likewise, the lime and sulphur content varied a great deal, a variation which could not possibly be due to the difference in the volumes of the solutions collected. Reference to the table shows that approximately 50% of the lime and sulphur were actually used in the preparation of the solutions.

Since nearly half of the original lime and sulphur remained after preparing the solution, it was decided to prepare another series of solutions starting with the same quantities of lime and sulphur, but increasing the quantity of water. The increase in the amount of water to be added was based upon the assumption that if starting with 1500 cc. of water and concentration to a total volume 1000 cc., an average of approximately 550 cc. of finished solution could be obtained, then by using 2250 cc. and concentrating to a total of 1450 cc. it should be possible to collect approximately 1000 cc. of finished product having a lime and sulphur content which, theoretically at least, would differ only slightly from the N. F. preparation. The results obtained are given in the following tables:

Solution No.	Cc. Collected.	% CaO.	% S.	Total CaO Gm.	Total S Gm.	% CaO Used.	% S Used.
7	922.5	10.18	16.20	93.85	149.36	56.87	59.74
8	990.0	8.4	15.08	83.16	149.29	50.40	59.71
9	950.0	8.96	15.48	85.12	147.06	51.59	58.82
10	875.0	8.12	14.86	71.05	130.02	43.06	52.07
Av.	934.3	8.91	15.40	83.29	143.93	50.48	57.47

The results show that by increasing the amount of water in order that the volume of the finished product would measure approximately 1000 cc. there was a decrease of nearly 5 per cent in the lime and nearly 10 per cent in the sulphur content. Taking into consideration the amounts of lime and sulphur actually used in preparing the solutions, it will be noted that whereas in the N. F. solutions about 46 per cent lime and 55 per cent sulphur were used, in this case the amounts dissolved in solution increased to an average of 50 and 57 per cent, respectively. Apparently, therefore, the addition of a larger quantity of water at the beginning of the preparation only slightly increased the total quantities of lime and sulphur which would go into solution. Under this condition it is obvious that the percentage strengths of the lime and sulphur would be much greater in the N. F. solutions.

Solutions were again prepared, this time the technique was varied as well as the amounts of the ingredients. Instead of adding the N. F. quantities of lime and sulphur to 1750 cc. of water and concentrating down to a total volume of 1000 cc., the formula was computed on the basis of a 1000 cc. of water added at the beginning. This required 94.28 Gm. of lime and 142.85 Gm. of sulphur. In order to maintain a constant volume, the mixture was boiled with a reflux condenser for three and one-half hours, the length of time required to prepare the solution accord-

ing to the N. F. directions. A volume of 950 cc. of finished solution was obtained which assayed 7.64 per cent lime and 11.68 per cent sulphur, thereby using up 77.21 per cent of the original lime and 78.14 per cent of the sulphur. Although the percentage strengths of the active ingredients were somewhat lower than the N. F. products, at the same time the total quantity dissolved was much greater. In using smaller quantities of the ingredients less liquid was held in contact with the residue thereby making it possible to collect nearly as much of the finished product as the original water added. By reducing the quantities of lime and sulphur to one-third the N. F. formula and adding 1000 cc. of water and preparing the solution in the same manner as the above, 932 cc. of finished product were obtained which assayed 4.34 per cent lime and 5.0 per cent sulphur. The total quantities of lime and sulphur dissolved amounted to 77.22 and 97.02 per cent, respectively. Decreasing the original quantities of lime and sulphur caused a corresponding decrease in their percentage in the finished product. It will be noted that practically all of the sulphur went into solution. Increasing the original quantities of lime and sulphur failed to materially increase their relative percentage strengths in the finished solution. This was shown by the fact that when 215 Gm. of lime and 326 Gm. of sulphur were used the per cent of lime and sulphur in the finished solution was 9.36 and 19.32 per cent, respectively. The total per cent of lime and sulphur used was 40.05 and 54.52, respectively. It is possible that a much larger quantity of soluble sulphides were formed but due to the bulk of the residue so much liquid was absorbed that the remaining liquid was insufficient to dissolve them.

In order to determine the amount of soluble sulphides which were presumably left in the residue after the preparation of the solution, and which were not dissolved, due to the lack of sufficient liquid, a series of solutions were prepared according to the N. F. directions.

The residue left on preparing the first solution was added to more water and the concentrating and boiling for one hour repeated, and so on; 1750 cc. of water were added in each case to the left-over residues in preparing solutions Nos. 5 and 6. In No. 12, 2250 cc. were added to the original ingredients; 500 cc. in 12*b;* and 1000 cc. in the cases of 12*c*, *d* and *e*. The following table offers a summary of the results of this experiment.

Solution No.	Cc. Collected.	% CaO.	% S.	Total CaO Gm.	Total S Gm.	% CaO Used.	% S Used.
4	590.0	10.90	22.30	64.54	131.57	39.11	52.62
5	650.0	8.60	7.79	55.90	50.60	55.64	42.72
6	740.0	5.72	2.64	42.32	19.53	94.97	28.79
12*a*	1085.0	2.52	1.69	27.34	18.33	16.57	7.33
12*b*	500.0	6.14	6.90	30.70	34.50	22.30	14.89
12*c*	985.0	3.86	2.54	38.02	25.02	35.54	12.68
12*d*	1050.0	3.50	0.52	36.75	5.46	53.30	3.17
12*e*	840.0	1.24	0.14	10.41	1.17	32.33	0.70

The results seem to indicate that a considerable quantity of sulphides can be dissolved by repeated treatment of the residues with water. Reference to solutions Nos. 4, 5 and 6 will illustrate this point.

From the residue left on preparing solution No. 4 there was obtained 8.60 per cent lime and 7.79 per cent sulphur, and when the residue from No. 5 was in turn treated with water and additional 5.72 per cent lime and 1.69 per cent sulphur was

recovered. There was dissolved, therefore, from the original residue left after the preparation of solution No. 4, a total of 14.32 per cent lime and 10.43 per cent sulphur in a total of 1390 cc. of finished product. Summing up, the original residue yielded a total of 25.26 per cent lime and 32.73 per cent sulphur by the foregoing treatment, and 1980 cc. of finished product were obtained. The series 12*a*, *b*, *c*, *d* and *e*, showed substantially the same results. As a result of repeated treatments of the residues in this series with water, 4460 cc. of finished product were obtained before practically all of the lime and sulphur in soluble form had been extracted. It will be noted that the final solution prepared, No. 12*e*, contained only a small amount of dissolved lime together with just a trace of sulphur.

It is quite apparent that the soluble sulphides, which were subsequently dissolved in the finished product by the repeated addition of water to the residues, were formed, during the concentrating and boiling of the original mixture, and that further treatment of the residue with water supplied the necessary solvent. If the assumption just made is correct a large quantity of the soluble sulphides, remaining in the residue after removal of the concentrated sulphide solution, could be obtained by washing the residue with additional hot or cold water. In this manner a definite quantity of finished product could be collected each time. It would seem that this procedure would be much more satisfactory than that of collecting only the liquid which separates from the residue, the amounts of which cannot help but vary each time the preparation is made. The N. F. directions specify that the mixture of lime, sulphur and water be concentrated to a volume of 1000 cc. and maintained at this volume, while boiling, for one hour. Experience has shown that it is quite difficult, if not almost impossible to keep the volume constant. The solution necessarily has to be prepared in large containers and any little variation in volume represents a relatively large increase or decrease in the amount of finished product obtained, and hence the percentage strengths of the lime and sulphur will seldom if ever be the same in different solutions.

This investigation is being continued. An analysis of the residues and of crystals forming in the solution is now being carried on.

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A COMPARISON OF RESULTS OBTAINED BY TWO METHODS OF INSTRUCTION EMPLOYED IN TEACHING PHARMACEUTICAL CHEMISTRY.*

BY CHARLES H. RODGERS.

In the presentation of the subject matter of any course of study an instructor is confronted with the pedagogical problem of how to present the particular course material in order to get the best results with an especial student group immediately at hand. To correctly determine what is the best method that should be used for a certain student group is not a simple matter, especially since the instructor usually has little or no advanced information on the average scholastic ability, coöperative desire and interest of the students in the group. An experienced instructor will

* Section on Education and Legislation, A. PH. A., Madison meeting, 1933.

usually "feel his way" with a new class, departing from the scheduled lecture and quiz periods by increasing the one and decreasing the other, as he thinks best, until he has found the combination that he believes to be the most satisfactory.

The problem is further complicated when the quantity of material covered by a course of study is very large and the number of lecture, quiz and laboratory hours assigned to the course is small. The course in which comparative studies of the results of several teaching methods has been made is designated as Pharmaceutical Chemistry. Three lectures, one quiz and three laboratory periods of fifty minutes each for the winter quarter of 12 weeks, and three lectures, one quiz and four laboratory periods of fifty minutes each for the spring quarter of 12 weeks, or a total of 180 actual hours, are allotted to this course. The course is intended to cover those facts about the elements and their compounds which are of especial interest to pharmacists. Such a consideration will naturally include official Latin and English titles, common names and synonyms, empirical and structural formulas, official definitions and rubrics, descriptions and physical properties, tests for identity and purity, pharmacological action of ions, chemistry of pharmaceutical preparations, industrial methods of manufacture, etc. The laboratory work includes the manufacture of a number of chemical compounds by processes as nearly like the actual industrial methods as possible. The student is provided with a textbook covering the material.

The vast amount of material in such a course precludes a *detailed* lecture presentation by the instructor and still reserves sufficient time for satisfactory quizzing and laboratory work. When the *most important* facts *only* are lectured upon and one oral or written quiz conducted once a week, it has been found that most students delay studying their notes made in lecture and also that portion of their texts covering the subject matter of the lecture until the evening immediately preceding the weekly quiz. This they *would* do despite advices to study concurrently with the lectures. This was proven time and again by giving unannounced quizzes upon the material presented in lecture on the preceding day and also by students confessing that they had to study in this way because of a heavy schedule. The average of student grades made on three unannounced written quizzes was about 62 per cent with only eighteen (18) making passing marks of seventy or better. However, when a similar quiz was *announced*, the general average was 79.2 per cent with only twenty per cent of the class having grades of less than 70 per cent but greater than 61 per cent (61%). When the same identical written quiz was given unannounced two weeks later, the examination average showed a general decrease of approximately 10 per cent. When given after four weeks, the decrease was only 12 per cent. Sufficient data were collected to show that announced quizzes given frequently had the coercive effect of making students study concurrently with the lectures.

The assignment of daily lessons from the text and utilizing the entire time scheduled for didactic work for oral quizzing was tried for several weeks. When questions dealing with O. L. T. formulas, common names, etc., were asked, the oral quiz marks were quite satisfactory. However, when the questions had to do with technology, ion actions, processes, etc., the answers showed a distinct lack of clear understanding. This emphasized the necessity of explanatory lectures on certain phases of the work.

During the third quarter of the 1932–1933 school year it was decided to try the following method. The daily assignment of work to be covered on both lecture and quiz days during weekly periods was posted on each preceding Thursday. Immediately upon reporting for class the students wrote a twenty-minute quiz on the material assigned for that particular day. The papers were then passed to neighboring students who corrected them during the next thirty minutes, which the instructor devoted to a lecture covering all of the questions asked in the quiz immediately preceding the lecture and, also, to any other material in the assignment needing explanation but not covered by the quiz. The papers were handed in at the close of the period and carefully reviewed by the instructor, who then returned them to the students for study.

After pursuing this plan (Plan A) for six weeks an examination on the subject matter covered in that time was announced. The average grades for these papers was 79.8 per cent. On the other hand, when three full period lectures and one oral quiz each week were given for six weeks (Plan B) and an announced quiz given on the material covered, the average for the class was only 62.56 per cent. When Plan "A" was employed, the student average grade on the announced quiz showed 17.24 per cent higher than that obtained when the second plan, "B," was used.

The estimate of time spent by students in the immediate preparation for the announced-written-quiz given after using Plan A was one and one-half ($1^1/_2$) hours per student. (Data obtained from approximately 50% of the students in the class —students selected at random.) Inquiries as to the time spent in the immediate preparation for the announced-written-quiz given after following Plan B showed an average of approximately three hours per student. There can be no question but that students spent more time in the aggregate preparing for the announced-written-examination given under Plan A and that this time was put in uniformly throughout the preceding six weeks (each night preparing for a 20-minute written test the following day), and furthermore resulted in obviating the necessity of devoting a long study period immediately before the written examination.

The "written-quiz-lecture" system, which we have used successfully, is not advanced as a new pedagogical method. As previously stated, it is the desire of every true teacher to use that particular method of presenting his subject which will result in the greatest benefit to his students. From the composite data collected to date, as well as from the observed general results, we believe that this method is by far the best one employed by us in teaching Pharmaceutical Chemistry. This plan does not necessarily work for other courses. For example, we have tried the method for several weeks in a course in Operative Pharmacy but have come to the conclusion that for this course the lecture-oral quiz plan gives better results.

It is our opinion that the written-quiz-lecture system is a mildly coercive way of inducing students to work for themselves and, when this is accomplished, the problem of the instructor is materially simplified.

Dedication of the American Institute of Pharmacy at Headquarters Building, Wednesday, May 9th, at 10:00 A.M.

DETERMINATION OF THE REASONABLE OR PERMISSIBLE MARGIN OF ERROR IN DISPENSING. II. OINTMENTS.*

BY MARVIN J. ANDREWS.[1]

INTRODUCTION.

In the first paper of this series,[2] a report was made of studies undertaken to determine the magnitude and frequency of errors made in the dispensing of powders and capsules. This, the second paper of the series, deals with the errors encountered in the dispensing of ointments.

Ointments called for on prescriptions are usually prepared by mixing the ingredients on an ointment slab or pill tile with the aid of a spatula. In some cases the nature of the ingredients make it necessary to use a mortar and pestle, and occasionally a slab and muller. The bases most frequently ordered are petrolatum, white petrolatum, lard, benzoinated lard, anhydrous lanolin, lanolin, a mixture of lanolin and petrolatum, or a mixture of the above bases. Ointments are usually dispensed in glass or porcelain jars, less frequently in collapsible tubes.

For the purpose of this study, the different types of ointment prescriptions which the pharmacist is ordinarily called upon to dispense were divided into three classes, namely: (1) Those which require no handling further than that necessary to transfer the ointment from a stock container to a dispensing jar. (2) Those in which compounding involves the incorporation of a liquid with a fatty or hydrocarbon base. (3) Those in which the compounding involves the incorporation of a solid with a fatty or hydrocarbon base.

With respect to the magnitude and frequency of the error to be expected in the dispensing of these three types, the capacity of the container, the base used, and the method of preparation of the ointment seem to be the most important factors to be considered. To determine the extent to which each of these factors contribute to the total error, the following studies were undertaken.

EXPERIMENTAL PART.

Three series of tests were made. The first series of tests was carried out using containers of different capacities, but made by the same manufacturer. The objective in this series was to determine the effect on capacity of the following conditions:

(1) Difference in nature of ointment bases. (*a*) Petrolatum, (*b*) lanolin, (*c*) lanolin and petrolatum, and (*d*) benzoinated lard were used for this purpose.
(2) Trituration of each of the above bases on an ointment slab for five- and ten-minute periods previous to packing.
(3) Incorporation of a liquid with each of the above bases.
(4) Incorporation of a solid with each of the above bases.
(5) Size of jar, that is half-ounce, one-ounce and two-ounce.

The principal objective of the second series of tests was to determine the varia-

* Section on Practical Pharmacy and Dispensing, A. PH. A., Madison, Wis., 1933.

[1] In collaboration with A. G. DuMez, Professor of Pharmacy, School of Pharmacy, University of Maryland.

[2] JOUR. A. PH. A., 22 (1933), 755, and 22 (1933), 838.

tion in the capacities of jars manufactured by each of the four manufacturers from whom they were purchased.

The objective of the third series of tests was to determine the variation in the capacities of jars purchased at random from retail pharmacists in the City of Baltimore.

In the actual performance of these tests, the ointment jars were filled in each case by 65 members of the senior class in dispensing pharmacy at the School of Pharmacy of the University of Maryland under working conditions similar to those prevailing in the better type of pharmacies. The filled ointment jars were checked for capacity by weighing on a prescription balance, and the standard deviation computed from the results obtained.

In the tests made to determine the variation in capacity due to the nature of the base, one series of jars was filled by melting and pouring the material into them, and a second series was filled by packing the base as received into them with the aid of a spatula. In filling the jars with melted base, the students were instructed to keep the temperature for melting as low as possible, and in the series filled with the base as received instructions were given to pack so as to eliminate air spaces in so far as possible.

TABLE I.—EFFECT OF DIFFERENT CONDITIONS IN PACKING OINTMENT JARS ON THE STANDARD DEVIATION.

Ointment Base.	Treatment and Packing.	½-Ounce Jar.	Average Capacity in Grains of 65 Jars.	S. D. in Grains.	Percentage Deviation.
Petrolatum	Packed solid	....	180	21.08	11.71
Lanolin	Packed solid	....	202	19.14	9.47
Lan. and Pet.	Packed solid	....	196	23.78	12.13
Benz. Lard	Packed solid	....	211	26.38	12.50
Petrolatum	Melted and poured	....	196	16.21	8.27
Lanolin	Melted and poured	....	216	14.89	6.89
Lan. and Pet.	Melted and poured	....	213	20.14	9.45
Benz. Lard	Melted and poured	....	199	26.23	13.18
Petrolatum	Trit. on slab 5 min.	....	178	18.65	10.48
Petrolatum	Trit. on slab 10 min.	....	177	19.50	11.01
Lanolin	Trit. on slab 5 min.	....	191	26.23	13.73
Lanolin	Trit. on slab 10 min.	....	185	24.09	13.03
Lan. and Pet.	Trit. on slab 5 min.	....	186	23.54	12.65
Lan. and Pet.	Trit. on slab 10 min.	....	184	26.80	14.56
Benz. Lard	Trit. on slab 5 min.	....	195	20.55	10.53
Benz. Lard	Trit. on slab 10 min.	....	187	24.01	12.84
Petrolatum	5% water incorporated	....	180	23.31	12.95
Lanolin	5% water incorporated	....	197	18.55	9.42
Lan. and Pet.	5% water incorporated	....	192	28.69	14.94
Benz. Lard	5% water incorporated	....	200	31.04	15.52
Petrolatum	5% ZnO incorporated	....	190	19.27	10.14
Lanolin	5% ZnO incorporated	....	207	24.57	11.87
Lan. and Pet.	5% ZnO incorporated	....	198	23.33	11.78
Benz. Lard	5% ZnO incorporated	....	210	22.95	10.93

It was assumed that the mixing of air with an ointment base would effect materially the weight of the contents of a jar filled with the base. To determine if this was actually the case instructions were given to triturate the above-mentioned

bases on an ointment slab with the aid of a spatula for 5- and 10-minute periods previous to packing.

In the tests intended to show the effect of the incorporation of a liquid with an ointment base, the students were instructed to use 5 per cent by weight of distilled water.

In the tests intended to show the effect of the incorporation of a solid with an ointment base the students were instructed to use 5 per cent by weight of zinc oxide.

In the filling of the jars students were instructed to put in an excess of material and level off the top by running the edge of a spatula over it. They were further instructed to remove any adhering material by carefully wiping the outside of the jar.

The results of the first series of tests are presented in Tables I, II and III.

TABLE II.—EFFECT OF DIFFERENT CONDITIONS IN PACKING OINTMENT JARS ON THE STANDARD DEVIATION.

Ointment Base.	Treatment and Packing.	1-Ounce Jar.	Average Capacity in Grains of 65 Jars.	S. D. in Grains.	Percentage Deviation.
Petrolatum	Packed solid	....	369	22.62	6.13
Lanolin	Packed solid	....	401	32.14	8.01
Lan. and Pet.	Packed solid	....	396	29.93	7.56
Benz. Lard	Packed solid	....	405	32.39	7.99
Petrolatum	Melted and poured	....	390	20.60	5.28
Lanolin	Melted and poured	....	417	26.24	6.29
Lan. and Pet.	Melted and poured	....	415	31.09	7.49
Benz. Lard	Melted and poured	....	397	39 04	9.83
Petrolatum	Trit. on slab 5 min.	....	354	31.35	8.86
Petrolatum	Trit. on slab 10 min.	....	355	31.63	8.91
Lanolin	Trit. on slab 5 min.	....	386	31.25	8.09
Lanolin	Trit. on slab 10 min.	....	373	36.80	9.87
Lan. and Pet.	Trit. on slab 5 min.	....	373	45.37	12.16
Lan. and Pet.	Trit. on slab 10 min.	....	370	47.10	12.73
Benz. Lard	Trit. on slab 5 min.	....	392	36.88	9.41
Benz. Lard	Trit. on slab 10 min.	....	374	38.28	10.24
Petrolatum	5% water incorporated	....	362	35.11	9.69
Lanolin	5% water incorporated	....	396	39.00	9.85
Lan. and Pet.	5% water incorporated	....	390	33.30	8.54
Benz. Lard	5% water incorporated	....	399	34.30	8.59
Petrolatum	5% ZnO incorporated	....	379	34.34	9.09
Lanolin	5% ZnO incorporated	....	411	37.48	9.12
Lan. and Pet.	5% ZnO incorporated	....	389	27.23	7.00
Benz. Lard	5% ZnO incorporated	....	408	40.27	9.87

The accompanying tabulations show that the average capacity in grains increases for the 65 jars packed with the solid base in the following order: petrolatum, 50 per cent mixture of lanolin and petrolatum, lanolin, benzoinated lard. When the base is first melted and then poured into the jars, the increase in the capacity of the jars is in the following order: petrolatum, benzoinated lard, 50 per cent mixture of lanolin and petrolatum, lanolin. Likewise, the jars when filled

by melting and pouring show a greater capacity than when filled with the same base by packing in the solid condition, except in the case of benzoinated lard.

The increase in capacity when the base is melted and poured is no doubt due to the fact that occluded air is driven out in heating, and to the fact that air-pockets are not formed in filling as is the case when the base is packed as solid.

TABLE III.—EFFECT OF DIFFERENT CONDITIONS IN PACKING OINTMENT JARS ON THE STANDARD DEVIATION.

Ointment Base.	Treatment and Packing.	2-Ounce Jar.	Average Capacity in Grains of 65 Jars.	S. D. in Grains.	Percentage Deviation.
Petrolatum	Packed solid	....	735	39.53	5.38
Lanolin	Packed solid	....	793	52.86	6.67
Lan. and Pet.	Packed solid	....	769	46.19	6.00
Benz. Lard	Packed solid	....	816	44.04	5.40
Petrolatum	Melted and poured	....	773	28.20	3.65
Lanolin	Melted and poured	....	831	34.51	4.15
Lan. and Pet.	Melted and poured	....	804	38.48	4.79
Benz. Lard	Melted and poured	....	774	55.32	7.15
Petrolatum	Trit. on slab 5 min.	....	712	58.62	8.23
Petrolatum	Trit. on slab 10 min.	....	707	54.31	7.68
Lanolin	Trit. on slab 5 min.	....	776	58.73	7.57
Lanolin	Trit. on slab 10 min.	....	752	57.92	7.70
Lan. and Pet.	Trit. on slab 5 min.	....	747	53.89	7.21
Lan. and Pet.	Trit. on slab 10 min.	....	730	54.39	7.45
Benz. Lard	Trit. on slab 5 min.	....	773	52.65	6.81
Benz. Lard	Trit. on slab 10 min.	....	741	68.18	9.20
Petrolatum	5% water incorporated	....	733	39.06	5.33
Lanolin	5% water incorporated	....	775	58.15	7.50
Lan. and Pet.	5% water incorporated	....	779	45.86	5.89
Benz. Lard	5% water incorporated	....	786	53.91	6.86
Petrolatum	5% ZnO incorporated	....	760	51.33	6.75
Lanolin	5% ZnO incorporated	....	808	57.63	7.13
Lan. and Pet.	5% ZnO incorporated	....	794	44.63	5.62
Benz. Lard	5% ZnO incorporated	....	819	48.65	5.94

The decrease in capacity when the jars are filled with benzoinated lard by melting and pouring is due, in part at least, to loss of water by evaporation. The expansion of the lard on heating also accounted for a part of the decrease in weight.

The standard deviation in the case of the jars filled with petrolatum, 50 per cent lanolin and petrolatum mixture, and lanolin is greater in each instance when the base is packed in the solid condition than when melted and poured. The magnitude of the error as shown by the percentage deviation varies inversely to the size of the jar.

The direction of the standard deviation in the case of the jars filled with benzoinated lard is directly opposite to that found for the other three bases, that is, the same volume of base weighs more when packed in the solid condition than when melted and poured in the jar.

The most important point brought out by the data in the above tables is that the frequency and magnitude of error is greater in the cases where the jars are filled with ointment in the solid state than in the cases where the filling is accomplished by melting and pouring.

Unfortunately, in actual drug store practice, the majority of prescriptions for

small quantities of ointments are filled by triturating the ingredients on a slab and packing the finished ointment into a jar with the aid of a spatula. This procedure is followed because the application of heat has a deleterious effect on the ingredients of certain ointments and because the preparation of an ointment by fusion requires that it be allowed to stand until it congeals before it is given to the patient, who is usually in the store waiting for it.

The tabulated data given above show further that the capacity of a jar by weight is decreased by triturating the ointment on a slab previous to packing in the solid state. No doubt this is due to the incorporation of air with the ointment base, thereby increasing its bulk and lowering its specific gravity. The time for which the material is triturated also seems to be an important factor, since in practically all cases the greatest decrease in capacity was shown where the period of trituration was ten minutes instead of five. In the case of benzoinated lard the fact that trituration results in liquefaction may also be a factor.

The incorporation of a liquid of comparatively low specific gravity and which does not readily mix with the base, such as water, appears to produce a decrease in capacity. The cause for this has not been definitely determined. It is believed, however, that the condition is due to emulsification and the occlusion of air. The effect produced by a liquid which is completely miscible with the ointment was not determined.

In cases where the specific gravity of the liquid is higher than that of the ointment base and where the liquid is insoluble in the base, an increase in capacity may be expected. In the case of the official mercury ointments, for instance, where the mercury content is high, the increase in capacity is enormous as shown in the following table.

TABLE IV.—CAPACITIES OF OINTMENT JARS FOR MERCURY OINTMENTS.

Size of Container.	Petrolatum.	Mild Mercurial Ointment.	Stronger Mercurial Ointment.
½-ounce	240 grains	343 grains	425 grains
1-ounce	480 grains	663 grains	838 grains
2-ounce	960 grains	1381 grains	1688 grains

In the case of the incorporation of a solid with the ointment base, it would naturally be expected that the capacity of the ointment jar by weight to be increased if the specific gravity of the solid were higher than that of the base and vice versa if it were lower than that of the base. The results obtained in the tests carried out with 5 per cent zinc oxide ointment show that these expectations are realized in so far, at least, as solids heavier than the ointment base are concerned. The increase in capacity, however, is not constant but varies with the ointment base used as shown in the above table. Evidently physical properties other than specific gravity are factors to be reckoned with, the solubility of the solid in the ointment base for instance. Unfortunately, tests were not made with solids lighter than the base, so that actual data on ointments of this type cannot be given at present.

For the purpose of making it possible to compare the results presented in Tables I to III with similar data that may have been published, but which have not been expressed in terms of the standard deviation, the per cent of deviation from the average has been calculated and is given in Tables V, VI and VII which follow.

TABLE V.—PERCENTAGE DEVIATION FROM THE AVERAGE WEIGHT OF ONE-HALF OUNCE JARS.

Ointment Base.	Treatment and Packing.	Average Capacity in Grains of 65 Jars.	Deviation from the Average Weight of 65 Completely Filled ½-Ounce Jars. 5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
Petrolatum	Packed solid	180	46.10%	30.76%	12.30%	6.15%	4.61%
Lanolin	Packed solid	202	70.75%	16.92%	6.15%	3.08%	3.08%
Lan. and Pet.	Packed solid	196	55.36%	16.92%	12.30%	.....	15.38%
Benz. Lard	Packed solid	211	63.06%	13.84%	7.69%	6.15%	9.23%
Petrolatum	Melted and poured	196	66.13%	15.38%	13.84%	.....	4.61%
Lanolin	Melted and poured	216	58.44%	29.22%	12.30%	.....	.....
Lan. and Pet.	Melted and poured	213	44.61%	41.53%	6.15%	1.54%	6.15%
Benz. Lard	Melted and poured	199	40.00%	24.61%	18.46%	6.15%	10.77%
Petrolatum	Trit. on slab 5 min.	178	38.45%	35.37%	12.30%	10.78%	3.08%
Petrolatum	Trit. on slab 10 min.	177	32.30%	27.68%	21.53%	7.69%	10.77%
Lanolin	Trit. on slab 5 min.	191	38.45%	26.15%	12.30%	10.77%	12.30%
Lanolin	Trit. on slab 10 min.	185	40.00%	24.61%	16.92%	6.15%	12.30%
Lan. and Pet.	Trit. on slab 5 min.	186	46.10%	26.15%	10.77%	4.61%	12.30%
Lan. and Pet.	Trit. on slab 10 min.	184	43.06%	30.76%	12.30%	3.08%	10.77%
Benz. Lard	Trit. on slab 5 min.	195	55.37%	24.61%	12.30%	3.08%	4.61%
Benz. Lard	Trit. on slab 10 min.	187	26.15%	29.22%	21.53%	10.77%	12.30%
Petrolatum	5% water incorporated	180	24.61%	29.22%	23.07%	10.77%	12.30%
Lanolin	5% water incorporated	197	43.06%	32.30%	16.92%	4.61%	3.08%
Lan. and Pet.	5% water incorporated	192	49.22%	33.84%	9.23%	3.08%	4.61%
Benz. Lard	5% water incorporated	200	53.83%	16.92%	12.30%	6.15%	10.77%
Petrolatum	5% ZnO incorporated	190	33.84%	41.53%	16.92%	6.15%	1.54%
Lanolin	5% ZnO incorporated	207	50.75%	27.68%	12.30%	4.61%	4.61%
Lan. and Pet.	5% ZnO incorporated	198	36.91%	32.30%	12.30%	6.15%	12.30%
Benz. Lard	5% ZnO incorporated	210	52.30%	23.07%	15.38%	3.08%	6.15%

In Table V, the percentage deviations from the average weight of ½-ounce jars show that in a large majority of cases the error is 15 per cent or greater, where the material filled into the jars was petrolatum, lanolin or 50 per cent lanolin and petrolatum mixture, and where the jars were filled by melting and pouring. If the filling is done by packing in the solid state, the error in the majority of cases is 20 per cent or more. If benzoinated lard is the base used, the error in the large majority of cases is 20 per cent or more, when the filling is done by either of the foregoing methods.

In Tables VI and VII, the percentage deviations from the average weight of 1- and 2-ounce jars, respectively, show that in a majority of cases the error falls within 10 per cent when the base is melted and poured into the jars, whereas the error is 15 per cent when the base is packed in the solid condition, or when other ingredients are incorporated with the base prior to transferring it to the jar. When benzoinated lard is the base used, the error is 20 per cent in the case of one-ounce jars, and 15 per cent in the case of two-ounce jars.

TABLE VI.—PERCENTAGE DEVIATION FROM THE AVERAGE WEIGHT OF ONE-OUNCE JARS.

Ointment Base.	Treatment and Packing.	Average Capacity in Grains of 65 Jars.	Deviation from the Average Weight of 65 Completely Filled 1-Ounce Jars. 5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
Petrolatum	Packed solid	369	63.06%	24.61%	9.23%	1.54%	1.54%
Lanolin	Packed solid	401	59.98%	24.61%	9.23%	.....	6.15%
Lan. and Pet.	Packed solid	396	55.37%	30.76%	7.69%	3.08%	3.08%
Benz. Lard	Packed solid	405	55.37%	32.30%	6.15%	1.54%	4.61%
Petrolatum	Melted and poured	390	79.98%	18.46%	1.54%	.....	.....
Lanolin	Melted and poured	417	69.21%	24.61%	3.08%	3.08%	.....
Lan. and Pet.	Melted and poured	415	67.67%	18.46%	10.77%	.....	3.08%
Benz. Lard	Melted and poured	397	64.60%	16.92%	10.77%	4.61%	3.08%
Petrolatum	Trit. on slab 5 min.	354	47.68%	26.15%	19.99%	6.15%	.....
Petrolatum	Trit. on slab 10 min.	355	44.60%	29.22%	19.99%	6.15%	.....
Lanolin	Trit. on slab 5 min.	386	50.75%	35.37%	6.15%	4.61%	3.08%
Lanolin	Trit. on slab 10 min.	373	46.10%	27.68%	13.84%	7.69%	4.61%
Lan. and Pet.	Trit. on slab 5 min.	373	53.83%	23.07%	10.77%	1.54%	10.77%
Lan. and Pet.	Trit. on slab 10 min.	370	55.37%	24.60%	6.15%	4.61%	9.22%
Benz. Lard	Trit. on slab 5 min.	392	55.37%	21.53%	12.30%	6.15%	4.61%
Benz. Lard	Trit. on slab 10 min.	374	38.45%	26.15%	13.84%	12.30%	9.23%
Petrolatum	5% water incorporated	362	44.60%	29.22%	18.46%	4.61%	3.08%
Lanolin	5% water incorporated	396	63.06%	24.61%	6.15%	1.54%	4.61%
Lan. and Pet.	5% water incorporated	390	56.91%	18.46%	16.92%	3.08%	4.61%
Benz. Lard	5% water incorporated	399	64.60%	18.46%	9.23%	4.61%	3.08%
Petrolatum	5% ZnO incorporated	379	53.83%	19.99%	16.92%	6.15%	3.08%
Lanolin	5% ZnO incorporated	411	61.52%	23.07%	7.69%	1.54%	6.15%
Lan. and Pet.	5% ZnO incorporated	389	55.38%	21.53%	15.37%	4.61%	3.08%
Benz. Lard	5% ZnO incorporated	408	58.44%	32.30%	1.54%	1.54%	6.15%

TABLE VII.—PERCENTAGE DEVIATION FROM THE AVERAGE WEIGHT OF TWO-OUNCE JARS.

Ointment Base.	Treatment and Packing.	Average Capacity in Grains of 65 Jars.	Deviation from the Average Weight of 65 Completely Filled 2-Ounce Jars. 5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
Petrolatum	Packed solid	735	70.75%	19.99%	7.69%	1.54%	....
Lanolin	Packed solid	793	61.52%	30.76%	4.61%	3.08%	....
Lan. and Pet.	Packed solid	769	61.52%	32.30%	4.61%	1.54%	....
Benz. Lard	Packed solid	816	69.21%	19.99%	7.69%	1.54%	1.54%
Petrolatum	Melted and poured	773	90.74%	6.15%	3.08%	....	....
Lanolin	Melted and poured	831	86.13%	9.23%	4.61%	....	....
Lan. and Pet.	Melted and poured	804	76.90%	16.92%	6.15%	....	....
Benz. Lard	Melted and poured	774	53.83%	29.22%	12.30%	4.61%	....
Petrolatum	Trit. on slab 5 min.	712	52.29%	24.61%	18.46%	4.61%	....
Petrolatum	Trit. on slab 10 min.	707	55.37%	30.77%	9.23%	4.61%	....
Lanolin	Trit. on slab 5 min.	776	59.99%	27.68%	6.15%	3.08%	3.08%
Lanolin	Trit. on slab 10 min.	752	90.74%	4.61%	1.54%	....	3.08%
Lan. and Pet.	Trit. on slab 5 min.	747	49.22%	33.84%	12.30%	4.61%	....
Lan. and Pet.	Trit. on slab 10 min.	730	59.98%	24.61%	7.69%	7.69%	....
Benz. Lard	Trit. on slab 5 min.	773	53.83%	33.84%	9.23%	3.08%	....
Benz. Lard	Trit. on slab 10 min.	741	30.76%	36.92%	27.69%	4.61%	....
Petrolatum	5% water incorporated	733	64.60%	27.68%	7.69%	....	....
Lanolin	5% water incorporated	775	55.37%	27.68%	12.30%	4.61%	....
Lan. and Pet.	5% water incorporated	779	64.60%	30.77%	3.08%	1.54%	....
Benz. Lard	5% water incorporated	786	61.52%	32.30%	6.15%	....	....
Petrolatum	5% ZnO incorporated	760	52.30%	30.77%	15.39%	1.54%	....
Lanolin	5% ZnO incorporated	808	61.52%	36.91%	.....	1.54%	....
Lan. and Pet.	5% ZnO incorporated	794	78.44%	13.84%	7.69%	....	....
Benz. Lard	5% ZnO incorporated	819	72.29%	18.46%	4.61%	4.61%	....

(*To be continued.*)

DISPLAY OF DENTAL ITEMS OF THE NATIONAL FORMULARY VI.

BY RALPH E. TERRY.*

Occupying a prominent space in the display of *Dental Pharmacology* at the Mid-Winter meeting of the Chicago Dental Society held at the Stevens Hotel, February 26th to March 1st, the Dental Items of the National Formulary VI attracted much attention. The Mid-Winter meeting of the Chicago Dental Society attracts members of the dental profession from the entire middle west, and visitors from the entire country. At the meeting just held, more than 3500 registrants were present.

As a part of the scientific exhibits, the College of Pharmacy of the University of Illinois prepared and displayed a number of materials of interest to dental practitioners. The exhibit was planned with the coöperation of Professor Gathercoal and Dr. Blayney of the Dental Sub-committee. It consisted of three sections and occupied 40 feet of wall space. Special glassware was provided for the exhibit and no expense was spared to make it as neat and attractive as possible. About one hundred placards were used, and nearly that many individual items were displayed.

One of the sections consisted of the mouth wash or rinse formulas suggested by Dean Geo. C. Schicks of Rutgers University, College of Pharmacy, who has been active in this work for some time. Three National Formulary items were used, Liquor Antisepticus, Liquor Aromaticus Alkalinus and Liquor Sodii Boratis Compositus. In addition, four mouth rinse formulas furnished by Dean Schicks were featured. Half-liter testing bottles were provided and small paper cups made it possible for those interested to test the products. Much interest was evinced over this section of the display.

The second part of the display consisted of a series of typical dental prescriptions such as analgesics, anodynes, sedatives, stimulants and local anesthetics. These were given on cards as formulas and the finished product was shown. In addition, a number of simples such as amyl nitrite, ether and other substances were shown. This section was planned by Dr. Blayney to demonstrate the proper manner of prescribing those official medicinal materials of value to the dentist.

The third section of the display consisted of the dental formulas of the National Formulary VI. Again the finished product was shown with the formula given on a card. Grouped around each product, the materials needed to make each formula were shown. This section of the display caused much interest, for the dental profession is becoming very much awakened to the need for knowing what it is using in the practice of dentistry. Dental preparations of the National

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Formulary were exhibited. The basic idea of this section was to bring to the dentist the work of the N. F. Dental Sub-committee to date that he might personally examine the preparations and note the formulas as recommended by this Sub-committee and now admitted to N. F. VI. A number of suggestions were made by various dentists regarding these preparations and their uses.

A four-page booklet describing U. S. P. and N. F. products of interest to dentists was published by the AMERICAN PHARMACEUTICAL ASSOCIATION and about thirteen hundred were distributed to interested dentists, care being taken to keep them from the general public. Many dentists were pleased to know that formulas for these preparations will be made available to them in the National Formulary VI, and a rather constant question was "when will the book be published?" Formulas of the booklet follow:

DENTAL PREPARATIONS OF THE NATIONAL FORMULARY EXHIBITED.

Anodyne Paste Dressing.—This contains Acetylsalicylic acid, Eugenol and Balsam of Peru, made up into a paste. Used as an anodyne dressing in painful tooth sockets.

Dental Liniment of Aconite and Iodine.—This formula contains Iodine, Fluidextract of Aconite and Alcohol. Used as a counter-irritant in acute, non-septic apical pericementitis. Cautiously paint on the gum to avoid undue absorption of an excessive amount of aconitine.

Dental Anodyne.—Oil of Clove fortified with chlorbutanol presents a splendid local anesthetic used for temporary relief in acute pulpitis.

Glycerite of Iodine and Zinc Iodide.—The zinc iodide and the iodine offer a stable astringent preparation possessing full antiseptic powers.

Camphor Phenol Sodium.—Phenol 30 per cent, Camphor 60 per cent and Liquid Petrolatum 10 per cent form a preparation highly antiseptic, yet devoid of topical irritation even to mucous membranes.

Aromatized Sodium Perborate.—The place of sodium perborate in dental practice is well established. The pharmaceutical problem of presenting this substance in an attractive form is solved by slightly sweetening with saccharin and flavoring with a volatile oil. A mint flavor is offered in the official formula.

Solution of Procaine Hydrochloride.—This solution contains 2 per cent of Procaine Hydrochloride in sterile normal salt solution. It can also be prepared with a suitable Ringer's Solution.

To each 10 cc. of the Solution, 0.1 cc. to 0.2 cc. (1 to 3 drops) Epinephrine Hydrochloride Solution is added just prior to injection.

Astringent Tooth Powder.—Add Copper Sulphate 2 to 3 per cent; or Zinc Sulphate or Zinc Sulphocarbolate 1 to 2 per cent; or Zinc Chloride 0.5 to 1 per cent.

Abrasive Tooth Powder.—Add Silex (xxx Flour) 25 to 50 per cent; or Pumice Flour 2 to 5 per cent.

Alkaline Tooth Powder.—Add Magnesium Oxide 20 to 40 per cent; or Sodium Borate 10 to 20 per cent; or Sodium Bicarbonate 50 per cent.

Oxidizing Tooth Powder.—Add Sodium Perborate or Magnesium Peroxide 20 to 50 per cent.

Dentifrice.—The following basic formula for a dentifrice produces a safe cleansing agent.

Soap, finely powdered	5.00%
Soluble Saccharin	0.25%
Oil of Peppermint	0.40%
Methyl Salicylate	0.80%
Precipitated Calcium Carbonate to make	100.00%

In turn, it may be medicated according to the needs of the patient by incorporating the active medicament in suitable quantity.

OFFICIAL SUBSTANCES AND PREPARATIONS EXTENSIVELY USED BY DENTISTS.

Abrasives and Cleansers.—Castile Soap U. S. P. X, Precipitated Chalk U. S. P. X, Pumice Flour N. F. V Silex (xxx Flour).

Analgesics and Anodynes.—Acetanilid U. S. P. X, Acetylsalicylic Acid U. S. P. X, Amidopyrine U. S. P. X, Chlorbutanol U. S. P. XI, Fluidextract of Aconite N. F. V, Oil of Clove or Eugenol U. S. P. X, Methyl Salicylate U. S. P. X.

Anesthetics (General and Local).—Chloroform U. S. P. X, Ether U. S. P. X, Ethyl Aminobenzoate U. S. P. X, Ethyl Chloride U. S. P. X, Nitrous Oxide U. S. P. X, Solution of Procaine Hydrochloride N. F. V.

Antacids.—Magnesium Oxide U. S. P. X, Magnesium Peroxide, Sodium Borate U. S. P. X.

Antiseptics.—Balsam of Peru U. S. P. X, Boric Acid U. S. P. X, Chlorothymol N. F. VI, Iodine or Tincture of Iodine U. S. P. X, Oil of Clove or Eugenol U. S. P. X, Phenol U. S. P. X, Sodium Perborate N. F. V, Thymol U. S. P. X.

Astringents, Styptics and Caustics.—Alum U. S. P. X, Arsenic Trioxide U. S. P. X, Glycerite of Iodine and Zinc Iodide N. F. VI, Glycerite of Tannic Acid U. S. P. X, Silver Nitrate U. S. P. X, Solution of Zinc Phenolsulphonate N. F. V, Zinc Chloride U. S. P. X, Zinc Sulphate U. S. P. X.

Cardiac Depressors (Vaso-dilators).—Amyl Nitrite U. S. P. X, Hypodermic Tablets of Nitroglycerin N. F. VI.

Sedatives.—Barbital Sodium U. S. P. X, Chloral Hydrate U. S. P. X, Sodium Bromide U. S. P. X.

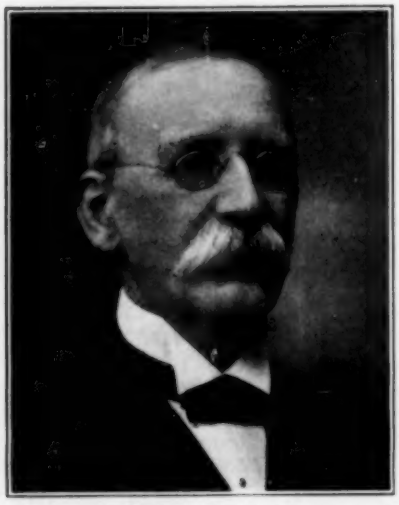
Stimulants (Cardiac and Cerebral).—Caffeine U. S. P. X, Camphor U. S. P. X, Hypodermic Tablets of Strychnine Sulphate N. F. VI, Solution of Epinephrine Hydrochloride U. S. P. X.

The sight of a thousand dentists industriously copying the formulas of the preparations exhibited was a pleasing one to the pharmacists serving at the display, for it proves that this phase of pharmaceutical activity has been neglected too long. Appreciative comments proved that dentists are interested in this sort of thing and exhibits of official substances should be continued at dental association meetings and expanded in the future.

The basic ideal of the entire display must not be overlooked, and this ideal as expressed in placards at the exhibit is to bring about "a closer coöperation between the dentist and his pharmacist."

DONATION OF DRUG JARS.

James E. Hancock has donated to the Museum of the American Institute of Pharmacy 22 glass drug jars, which were owned by his father, the late John F. Hancock, president of the AMERICAN PHARMACEUTICAL ASSOCIATION, in 1874.



JOHN F. HANCOCK.

The bottles are 16 inches high and 7 inches in diameter, each container carries the coat of arms of a state; the design is a work of art in gold and pigment, below it is the name of the drug which the jar contained and gives to the container its coloration; thus, sulphur—yellow; indigo blue, etc. These jars are rare and date back to the time when only twenty-two states had been admitted to the Union; probably, nowhere is as complete a set and in such perfect condition as represented by this collection.

The ASSOCIATION will also receive from the same donor copies of "Theophrastus" and of "Valerius Cordus," both in excellent condition.

W. F. Thiede is the present owner of the John F. Hancock Pharmacy at 1501 E. Baltimore Street, Baltimore; few changes have been made in it, honoring the memory of his predecessor, who carried on his prescription practice in full view of the public; the furniture of this department is of walnut and in this as well as other sections of the pharmacy original ideas of the founder are in evidence.

The American Institute of Pharmacy is dedicated to those who have given of their thought and endeavor to the preservation of Public Health and to the further advancement of Science in Pharmacy.

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

Editor's Note: Some of us may think that the old days when we were compelled to teach incompatibilities for hours on end have gone and we need to give little or no attention to the subject to-day. With better basic training being given our students, we would not have to give as much time to this subject as we used to give in the past. However, we must not lose sight of the fact that new incompatibilities are arising every day because new drugs, especially new synthetics, are being introduced. Prof. Mantz sets forth these problems in a clear and lucid way and offers a good suggestion on when and how the subject should be taught.—C. B. JORDAN, *Editor.*

WHEN SHOULD THE COURSE IN INCOMPATIBILITIES BEGIN AND HOW SHOULD IT BE TAUGHT?

BY HARRY W. MANTZ.*

The methods used in teaching incompatibilities are, no doubt, similar in all schools of pharmacy. Assuming this to be true, any useful methods carried out in one school can be applied advantageously by the others, and I present this paper with the hope that it will give rise to discussions from which we may all profit. No matter how efficiently this subject may be taught, there will always be room for improvement.

Incompatibility is one of the most difficult and most inadequately taught subjects in a pharmacy school curriculum and it is my thought that if a teacher is honest with himself, he cannot have a feeling of complete satisfaction after he has finished his discussions of the subject. I am not criticizing the ability and knowledge of the teacher but refer to the difficulties inherent in the subject itself.

Scientific, as well as commercial progress, leads to discoveries and the production of new compounds to be used for the cure of disease, which causes a continual increase in the scope of the subject. This is further complicated by the fact that little is known about the composition of many of the so-called proprietary preparations, so frequently prescribed and this makes it difficult to explain many incompatibilities which may arise in combinations containing such products.

In order to get a picture of the magnitude of the problem facing us, let us consider the number of prescriptions which could be written, by using one hundred drugs with "four to a prescription." The number of different combinations obtainable amount only to a little less than four millions. Now, if we were to include all the medicinal substances known, the total would probably make the war debt figures, which we see in the daily newspapers, look like pin money. This gives us an idea of the potential difficulties which may be dormant, but which may suddenly come into existence and face the man in the prescription laboratory. Therefore, as teachers, we feel it our duty to train the students so that they will be able to cope with these problems when they arise.

Referring more specifically to the subject of this paper, "When Should the Course in Incompatibilities Begin and How Should It Be Taught?" the syllabus allots 64 didactic hours and 128 laboratory hours to Dispensing Pharmacy and

* Temple University.

suggests the teaching of incompatibilities as a part of the course. While we understand the subject had to be put under some heading, we feel that this particular branch in the training of a pharmacist is of such vital importance that it cannot be adequately taught as a subdivision of Dispensing Pharmacy during the number of hours suggested. Pharmacy as an art comes into being in the dispensing laboratory where the final technique is affected. At this stage the student is on the verge of putting into practice, in his chosen profession, the knowledge which he has accumulated. When this part of his training has been reached, he should have a knowledge of incompatibilities and be able to apply it.

Instead of being incorporated as a part of a single subject, incompatibilities can be taught more effectively by dividing them into the three classifications and enlisting the coöperation of the chairs of Chemistry, Pharmacy and Pharmacology. The teachers should have two objectives in view: *first*, to teach so that the students will gain a fundamental knowledge of their subjects, and *second*, with the idea of training them to use such knowledge as it applies to incompatibilities. We all realize that students generally lack the ability to apply what they have learned. This teaching should begin as soon as the students have an understanding of the various subjects sufficient to enable them to comprehend the meaning and importance of incompatibilities as they pertain to medicinal substances.

The teaching of chemical incompatibilities can have its origin in General Chemistry under the discussions of ionization, and be continued throughout the various succeeding courses in Chemistry. In the laboratories prescriptions can be used to illustrate the reactions. For example, in giving the test for chlorides, a prescription containing silver nitrate and physiological salt solution could be used to make the student aware of the incompatibility which exists in such a combination.

Discussions on pharmaceutical or physical incompatibilities can be included with those of the simplest preparations such as the aromatic waters. In the laboratory the student can compound a prescription calling for a bromide to be dissolved in an aromatic water and note what occurs, and then be instructed how to remedy this difficulty. In like manner, the student could be gradually trained to handle the more difficult combinations.

The pharmacist is not greatly concerned with therapeutic incompatibilities, but the departments of Pharmacology and Toxicology could do their share of the work by referring to the poisonous combinations which may result from chemical changes or unforseen physical incompatibilities.

By following these plans the teachers in the laboratories have the opportunity of applying one of the basic principles of learning, "Learn by Doing," and we all agree with the old saying, "Experience is the best teacher." This is really how our veteran forefathers in pharmacy learned their profession; they learned by doing. Due to the change of conditions in the profession of pharmacy and to the gradual decrease of practical experience required by the State Boards, the burden now rests upon the shoulders of the institutions and their faculties. They are expected to supply ways and means for this training.

These are the methods the School of Pharmacy of Temple University uses to teach incompatibilities before the student enters the course in Dispensing Pharmacy.

Allow me to explain briefly how we teach that part of Dispensing Pharmacy which applies to incompatibilities and the compounding of prescriptions. At this point we know that the student has had instruction pertaining to incompatibilities both in lectures and in laboratories. The Dispensing Pharmacy Laboratory, as has been stated, is the finishing department and the work outlined here for the students, as far as this subject is concerned, consists chiefly of an application of the knowledge already gained.

We have on file the names of approximately one hundred practicing physicians from whom we solicit prescriptions which they use frequently and we request them to mark those which they have found by experience to have been the most difficult to have compounded satisfactorily. This list not only includes physicians in the vicinity of Philadelphia, but those located in different sections of Pennsylvania and a few other states. Many names and addresses of physicians are obtained from the students themselves.

The prescriptions are placed on cardboards which are inserted into a folder with a leather back and transparent front, and each student is required to copy the prescriptions in a note-book. A certain amount of time is set aside during each laboratory period for this work. After each student has copied about two hundred prescriptions, he is assigned four on which he writes a detailed description as to the methods of preparation of the ingredients, the methods of compounding and a discussion of any difficulties which might possibly arise. This procedure makes it necessary in many cases for the student to refer to the library. At the end of the time allotted, each student reads his assignment in class. The instructor then answers questions, makes corrections or further discusses the prescriptions, as necessary. In this manner each student contributes to and benefits by the research work of the others. Many of these prescriptions are compounded during the laboratory hours. It is interesting to know that in many cases those students who are working in drug stores compound the prescriptions assigned to them for their own benefit, if they have not been already compounded in the dispensing laboratory. In other cases exceptional prescriptions are compounded by the instructor to demonstrate the reactions.

Our curriculum contains special hours assigned to the general discussion of difficult prescriptions received in drug stores where our students are employed. The students also are urged to make memoranda of any interesting problems which only present themselves in a drug store. During this period a representative from each of the departments of Chemistry, Pharmacy and Pharmacology is present to discuss questions which are pertinent to his teaching.

By using this system we feel that the student is getting experience which is analogous to that obtained in a drug store. He comes in contact with prescriptions which are being used rather frequently; and due to the number of physicians who submit them, he gains valuable experience in reading a variety of handwritings.

With the trend of modern medicine toward the use of specifics in the treatment of disease, these problems may not confront the pharmacist in the future as frequently as they have in the past. For the present, however, as teachers, we should feel it our responsibility to give the student training which is as practical and comprehensive as possible.

To summarize, my thought is that

1. Teaching incompatibilities should begin soon after the student enters the school.

2. All teachers should have this subject constantly in mind and select illustrations for their statements from the incompatible group whenever possible.

3. This accumulation of theory under the various chairs should then be applied in the course of dispensing pharmacy.

4. Better results will be obtained from the use of original prescriptions than from the use of printed formulas.

5. The conference on prescription difficulties occurring in the stores from day to day, keeps the instruction up to the minute.

THE TEACHING OF INCOMPATIBILITIES.

BY W. G. CROCKETT.*

Editor's Note: The preceding paper by Professor Mantz, together with the four papers following, comprise a good symposium on Incompatibilities. It is noticeable that the authors are not in entire agreement on when and how this subject should be taught and this, to me, is a good sign. When we all agree on a time or a method of teaching a subject, we should ask ourselves whether we have not eliminated originality, the teacher's best qualification. Two teachers may present a subject in quite a different way and yet secure equally good results. I do not agree with some of the authors on when and how incompatibilities should be taught and more than likely the reader would not agree with me should I set forth my opinions. What are we to do in this dilemma? Read all the papers, those of Mantz, Crockett, Johnson, Mitchell and Terry, and cull the best from each of them.—C. B. JORDAN, *Editor.*

The subject of incompatibilites in prescriptions is an important one, and one which should not be treated superficially by educators merely because physicians in recent years have become more and more inclined toward prescribing simple-named, manufactured products. Evidences of closer coöperation between medical and pharmaceutical groups throughout the country, along with increasing costs of medical care, lead me to believe that as the years go by physicians will return to writing original prescriptions in order to reduce the costs of medical care and at the same time forestall self-medication on the part of the laity. If this be true the subject of incompatibilities in prescriptions will be of more concern in years to come than it is at the present time. We must teach for future needs as well as for present ones.

A complete discussion of the teaching of incompatibilities should embrace both what to teach and how to teach it. This subject is so broad and so debatable that I shall not attempt to treat either of these phases in detail, but instead will confine myself to a few thoughts or principles with the expectation that the discussion which follows will bring us many different points of view and thereby be more helpful than my own personal views. Any scheme I might present would prove inadequate even to myself. I say this because I find myself altering my own approach to the subject from year to year.

At the outset I wish to state that I think it a mistake to isolate the subject of incompatibilities and attempt to teach it as a separate course. Curricular

* Medical College of Virginia.

conditions in the three-year course necessitated my attempting it in this way. I found that the students regarded it as a separate entity and failed to associate it properly with dispensing pharmacy. I think the didactic and laboratory courses in dispensing pharmacy should treat first of the fundamentals of prescription compounding with emphasis upon technique and the many minor but important details. The subject of incompatibilities should develop out of this course, as a part of the course in dispensing pharmacy. The discussion of prescriptions in both didactic and laboratory courses should be complete. If the subject of incompatibilities is segregated and taught as a separate course under a distinctive title the student is inclined to magnify the importance of the incompatibility, and in his discussion neglect such vital points as the method of compounding, accessory labels and the kind of container in which the prescription should be dispensed.

I think a review of the pertinent parts of qualitative analysis is highly advisable. I can go further and give you an outline of the method which I followed last year. I distributed sets of mimeographed sheets to the students, bearing the more important incompatibilities of the common inorganic and organic compounds. I made assignments on these sheets and at the following didactic period distributed prescriptions which set forth incompatibilities mentioned in the assignments. These the students discussed both orally and in writing. Afterward they compounded some of them in the laboratory.

After the sheets had been disposed of, I distributed at each didactic period copies of prescriptions representing incompatibilities in general. The students were required to discuss them fully, both orally and in writing, during that particular period. Results were gratifying. I have been unable to get satisfactory results in prescription discussion by making assignments in a book which points out the incompatibilities, their remedies and methods for compounding. Conferences with students after graduation have confirmed my belief that this is poor practice, as it tempts students to memorize rather than think.

It is of course understood that teaching problems differ in different institutions. In writing this paper I have been influenced undoubtedly by conditions in the institution which I represent. A brief explanation may be in order. The Medical College of Virginia operates two dispensing pharmacies to take care of the needs of its out-patient department and three hospitals. The medical staff rotates, thereby bringing approximately 150 physicians onto the staff during the year. Practically all the prescriptions written by these physicains are for official and extemporaneous mixtures. The ordering of medicines by stock numbers is not permitted. All prescriptions are written just as if they were to be presented at a retail store.

Approximately 150 prescriptions are filled daily in these two pharmacies. Routine prescriptions which do not constitute experience for students after they have filled them two or three times, are segregated and filled by the full-time hospital pharmacists. The others are filled by senior pharmacy students, under close supervision. In the past each senior student has served fifteen hours a week for approximately ten weeks in these dispensing pharmacies. Now that classes are smaller their periods of service will be lengthened. These facilities have enabled us to give much instructional work in incompatibilities in these pharmacies, as

each student is quizzed on each prescription he fills as soon as it is completed. This course is supplemented by a laboratory course in prescription compounding, in which types of incompatibilities which do not occur frequently in our dispensing pharmacies, are treated.

These articles will be continued in the May number of the Journal.

THE NATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH.

BY JOHN C. KRANTZ, JR., SECRETARY.

The National Conference on Pharmaceutical Research has sent out its official notices convoking the Thirteenth Annual Meeting. This meeting is to be held in conjunction with the AMERICAN PHARMACEUTICAL ASSOCIATION at the Hotel Shoreham, Saturday, May 5th, at 2:00 P.M.

During the thirteen years of its existence the National Conference on Pharmaceutical Research has served as a clearing house for research in pharmacy and its cognate sciences in the United States. It has annually compiled a Census of Pharmaceutical Research which has been most useful in determining the increment of progress of research in pharmacy during the year. Besides, this census serves as a stimulus to research workers in the field. In addition, under the auspices of the Conference, the Symposium "Fighting Disease with Drugs" was published for the purpose of telling the story of pharmacy in a more or less popular style.

For the past two years the Conference has awarded annually a fellowship of five hundred dollars to graduate students in universities pursuing courses for the doctorate degree, whose research was of a pharmaceutical nature.

During the coming year the Conference will endeavor to compile the reports of the various committees, written in a simple, narrative form, in a volume indicated as The Annual Survey of Pharmaceutical Research. It is our hope that this new publication will adequately tell the story of the advance in pharmacy each year and like the Census of Research serve as a stimulus to workers in the field.

The Conference anticipates a successful meeting in Washington, and takes this opportunity to invite those interested in the various ramifications of pharmaceutical research to attend its sessions and to participate in its deliberations.

RESEARCHES AT THE MELLON INSTITUTE.

Among the results of the investigations it has been determined that no systemic pharmacological effects can be ascribed directly to absorbed aluminum; it does not appear to be cumulative in the tissues. No harmful effects were shown from soluble aluminum occurring naturally in foods or from utensils.

Recent investigations which are being carried on with the coöperation of Mellon Institute have indicated probable valuable application of sodium metaphosphate in the field of veterinarian medicine. One of its uses is for preparing solutions for washing and rinsing dogs and other furred animals.

WASHINGTON BOTANIC GARDENS.

Development of the old site of the Botanic Gardens into Union Square and the proposed transfer of the new Botanic Gardens from jurisdiction of the Joint Committee on the Library of Congress to the Department of Agriculture recall the origin and development of this old institution, which has been in existence for more than a century.

The establishment of a botanic garden was the subject of correspondence between Washington and District of Columbia officials. It was in 1820, after years of discussion, that the Columbian Institute for Promotion of Arts and Sciences obtained passage of a bill in Congress, which became a law on May 8th.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter.

BALTIMORE.

The regular monthly meeting of the Baltimore Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at the Hotel Emerson on Tuesday, February 27, 1934.

President Cole opened the meeting and the usual business was deferred. The meeting was turned over to Mr. John A. Strevig, of Eli Lilly and Company, who presented a sound film entitled, "The Production and Clinical Application of Insulin."

The picture portrayed the various steps in the production of insulin on a huge scale, the numerous control procedures involved, and the final standardization of the product. The second portion of the film was devoted to the application of insulin in the treatment of the diabetic in the clinic. One of the most interesting exhibits presented was a young man who has received as many as ten thousand injections of insulin in the past ten years without infection from the injections. A truly remarkable record for a remarkable drug.

At the conclusion of the presentation a rising vote of thanks was extended to Mr. Strevig and the company which he represents. About seventy-five attended the meeting.

MARCH MEETING.

The Baltimore Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was host to the members of the Boards of Pharmacy and the Faculties of the Colleges of Pharmacy in District No. 2 at their March meeting.

The evening was devoted to a dinner given in honor of the visiting members of these associations. The dinner, held at the Emerson Hotel, was an unusually delightful affair. The speaker of the evening was Dr. Huntington Williams, Commissioner of Health of Baltimore City, who had for his topic, "Relation of Pharmacy to Public Health." Many notable personages in pharmacy and medicine were present. After the conclusion of Dr. Williams' address President Cole called upon many of the deans of the Colleges of Pharmacy and others for a few remarks which were rendered in a humorous manner with due attention to the more serious nature of the meeting.

Approximately fifty guests attended the dinner meeting and also a number of the local members of the Baltimore Branch, A. PH. A. The address by Dr. Huntington Williams follows:

RELATIONSHIPS BETWEEN PHARMACY AND PUBLIC HEALTH.*

BY HUNTINGTON WILLIAMS, M.D., DR.P.H.

Medicine and Pharmacy are sister sciences which have traveled hand in hand down the centuries from prehistoric times and ever since self-preservation has been instinctive in the human

* Address delivered before the Boards of Pharmacy and the Faculties of the Colleges of Pharmacy in District No. 2, Baltimore, Maryland, March 12, 1934.

race. Preventive medicine has an equally long heritage, but only recently has it emerged as a full-fledged specialty in the medical family, with new scientific bases and techniques of its own. The aims of medicine and pharmacy have always been the same; namely, the protection or restoration of health. Of late, however, there has been established a new focus of attention, the *keep-well* rather than the get-well point of view. And now in 1934 we find ourselves five years along in a new era, faced with new problems resulting from a world apparently out of gear—a topsy-turvey world created, it seems, from the golden prizes which human greed and selfishness have ever held just out of reach. If ever there was a time when teachers were needed to set an example and stress the return to the old-fashioned ideals of unselfish service, it is now. With this thought in mind, I would direct your attention for a few moments to some of the mutual relationships between public health and pharmacy.

The goal which modern medicine is gradually setting for itself, which indeed the intelligent modern layman is demanding of it, is a *keep-well* service, which from the prenatal period to the grave seeks to prevent needless sickness and suffering and to postpone the arrival of the grim reaper just as long as possible. Whereas the old-style public health was largely a restrictive or *police* type of service, based on inadequate scientific knowledge; the modern health movement is almost entirely *educational* in its viewpoint. The health officer of to-day tries to teach his people the thousand important ways of keeping well.

It would seem that in pharmacy, too, the National Association of Boards of pharmacy has recognized the need for spreading the newer information and has established a Department of Education which issues a special Bulletin. When the health officer looks about him he sees at once that he is faced with a mammoth task—to achieve success it is imperative that the teaching of the essentials of keeping well must be integrated into all the educational processes going on about him. Their range is rather staggering. This evening I would emphasize one of the special educational fields in which adequate public health instruction is essential and in which a closer liaison may perhaps be built up between pharmacy and public health.

This special field is that of higher or professional education, the field which, for our purposes includes the medical schools, and the schools of nursing, dentistry and pharmacy. In this field the opportunities have never been greater nor the responsibilities more definite for placing in proper focus in the curriculum the attention which should be paid to instruction in public health and the modern aspects of preventive medicine.

To-day the graduates in all these special groups are expected to practice their professions along preventive lines. To do this each group must know much of the principles of the modern public health movement, which is so wide in its scope as to embrace the preventive aspects of all the special fields. The curricula of these professional schools are rapidly expanding to include the *keep-well* viewpoint. The tremendous need for this in schools of pharmacy is clearly expressed in the following statement taken from the introduction to a volume known to most of you here to-night, "The Basic Material for a Pharmaceutical Curriculum:"

"Conspicuous among the duties of the pharmacist is the group which deals with public health. These activities constitute his major function in connection with social and community life. Filling prescriptions correctly is, of course, important to the public, as is also the display and sale of reliable products; but in the service to public health the pharmacist serves the community in a unique way. Naturally, there are many sources from which the public may secure accurate health information—the public schools, the newspapers, and the publications of federal, state and private agencies. These all contribute their part to the solution of health problems; but the information they provide is general, and must be made specific in order to meet the personal needs of the one who is confronted with specific troubles of his own. To give this personal assistance the doctor is at hand. But many people are afraid of physicians and hospitals. Moreover, the physician keeps office hours which are relatively inconvenient for people who are busy with their own affairs. In addition to this, charges for consultation and treatment, even though modest, often keep the public from seeking the advice of a physician.

"The pharmacists are therefore more strategically situated than any other group of individuals to give personal advice upon matters of public health on which they are informed. The information is given free of charge and can be secured within easy walking distance of the home. The materials necessary for controlling the health problem are in stock and can be obtained promptly. Queries about health facts are casually asked by interested customers. Odds and

ends of information not easily accessible in the health literature can be gained in such conversations with a pharmacist. A well-informed pharmacist is the best single individual to disseminate information about public health."

Certainly if this be true a tremendous responsibility rests upon those persons who are charged with the training and licensure of future pharmacists and the post-graduate instruction, such as there may be, of those now in the field. You who are the ones to shoulder such a burden in this portion of the country should find the health officers and their colleagues in the medical profession more than willing to aliy themselves with you in a common purpose.

What are some of the practical ways in which the graduate in pharmacy may best fit himself into the public health machinery of his own community? First of all, I feel that the man in charge of a corner drug store would want to select from his acquaintance some particular physician in whom he has great confidence and to whom he would feel free to turn for suggestions and guidance in the many problems of his daily work that may have a direct bearing on the practice of medicine, both curative and preventive. Then, I believe the pharmacist would wish to establish a personal relationship between himself and some representative of the local health department or board of health in his community so that by informal telephone communication he would, at any time, be able to secure the point of view of the official health authorities on a multitude of problems closely connected with his own work.

What are some of these special public health problems which day after day confront the man behind the counter? Among the very first should probably be mentioned the matter of the venereal diseases, which probably is the biggest and most difficult of all public health problems. Here again the volume on basic curriculum material in pharmacy includes the following wise statement:

"The venereal diseases annually exact an enormous toll of health, happiness and efficiency. The very great frequency with which pharmacists are consulted with respect to the treatment of these diseases places them in a special class from the standpoint of a student of pharmacy. Probably there is no public health problem in the solution of which the coöperation of the pharmacist is so desirable as the education of the public with regard to the dangers of these diseases and the importance of observing the laws and ordinances promulgated for their control."

The prevalence of the venereal diseases in our community was recently studied in a careful manner by the United States Public Health Service, with the resultant estimate of approximately 10,000 fresh cases of venereal diseases in this city each year and an approximate total of 10,000 cases constantly under treatment in this city. Health officials are still baffled in many communities by what amounts to a conspiracy of silence in connection with this problem and by a great public apathy in regard to it. Gradually, but by very slow educational methods, we are striving to reach a more open-minded public approach to this great question. In the meantime we know of the tremendous temptations which beset the pharmacist for "over the counter" diagnosis and treatment by the promiscuous sale of remedies of doubtful value. The man behind the counter, of course, should do his best in determining whether his client can afford a family physician and in obvious cases where this is economically impossible, the pharmacist should know of the nearest health department venereal disease clinic or hospital dispensary and refer his customer to it.

In the matter of tuberculosis we are faced with somewhat the same problem. The patent medicine and the cough mixture are easy to dispense, but the pharmacist who takes his responsibility seriously will worry considerably as to whether the cough or cold has been of long duration and again should know of some tuberculosis clinic or dispensary in case his client is apparently an indigent. It was not many months ago that I stopped at a corner drug store one evening and witnessed a young assistant in charge, scarcely more than twenty years old, who took from the shelves what was apparently a patent preparation for a customer who said he had a pretty bad cough. Just which of a large variety of commercial products was to be selected was determined by the remark of the young fellow behind the counter that he knew this particular brand was said to be useful in "lubricating the bronchial tubes." This settled all questions in the mind of the purchaser who went away satisfied, although I left with a feeling that the bronchial tubes were not just like a set of piston rings, in need of lubrication.

The pharmacist comes close to the public health program in the matter of the handling and distribution of many biologic products, such as sera, antitoxins and vaccines. For ten years it was my official duty to make periodic inspections of public health laboratory supply stations,

established in drug stores, and I was constantly amazed at the indifference with which some very perishable biologic products were stored in an ice-box, it would seem merely for the sake of appearances and quite regularly without the use of ice. It certainly must be true that many young children are vaccinated time and time again without success, because the vaccine virus has not been kept on ice either at the pharmacy or in the physician's office.

Of course the public will ask at the drug store for all types of information on personal hygiene, including the prevention of such diseases as diphtheria and typhoid fever. I see no reason why an up-to-date pharmacy should not have a rack accessible to all its customers, which might be filled with a carefully selected set of leaflets and pamphlets issued by the recognized health authorities and prepared for free public distribution as high grade educational material on these and many other problems of personal and community health. Again the customer will ask for the latest information in regard to nutritional problems, which brings up the whole matter of an apparent present-day tendency to overadvertise the vitamins. In this field I have a strong feeling that the whole vitamin business has been so thoroughly and unjustifiably commercialized with the misleading advertising which is so rampant in our day, that modern scientific developments are often asked to bear premature and excessive burdens. This same feeling would apply in like manner to a host of other problems which face the pharmacist in his daily work and which we trust may, in some manner, be improved by the enactment of a new federal food and drug bill.

The pharmacist is called upon at any hour to render first aid and of course must always have a knowledge of toxicology which often has an important bearing on preventive medicine and public health. So, too, he must have a knowledge of the essentials of maternal and child hygiene as well as a general understanding of the practical problems of community sanitation, including the purity of public water supplies and of milk and food supplies.

It would be a needless task for me to attempt to bring before you any complete review of the endless inter-relationships between the work of pharmacy and public health. You will agree, I feel sure, that to instil into the pharmacist a desire for a thorough knowledge of the modern public health campaign is really about all that is necessary. If he does not lose this desire, he will continue to keep up-to-date and be a most valuable member in the great army of public health workers in his community. There can be no doubt that in this matter all of us have a great and common task which is largely educational in nature. Concerning it, I, for one, am filled with optimism for the future.

The lessons of the last five years have been hard, but necessary ones. The period since 1929 has been one of a great awakening—and came at the end of a decade when all classes were worshiping the golden calf. The house of cards has pretty well fallen and with the depression may come a return of common sense, and a desire to understand and coöperate for the public good. Evidences of such a tendency may already be seen in the proposed changes in the national food and drug bill, which will be supported by the sister sciences of pharmacy and public health. As Dr. Robert Swain has pointed out—legislation in pharmacy as in other fields should be based on sound public interest and not on selfish motives. It is not too much to hope for a clearer focus on spiritual values in our every-day work where much will depend on the honor and integrity of the individual. We may be well-content to follow the way of life of perhaps the greatest modern physician, William Osler. He did his day's work as best he knew how and was willing to leave to destiny the outcome of his labors.

CHICAGO.

The monthly meeting of the Chicago Branch was held on March 20, 1934, at the University of Illinois, College of Medicine.

A "Symposium on Hospital Pharmacies" was presented by the following active members of the Branch: Wm. Gray of the Presbyterian Hospital, I. A. Becker of the Michael Reese Hospital, S. W. Morrison of the University of Illinois Research Hospital.

The discussions brought out the many differences between the hospital pharmacies and the retail drug stores. The number of prescriptions filled calls for the purchasing of drugs in large quantities. A comparison of the relative value of a drug as compared to another similar acting drug of less cost must be made as the hospital expense for drugs can be materially lowered where such large amounts are used.

Definite systems in the filling of the prescriptions are used to promote efficiency, accuracy and time saving.

Mr. Becker mentioned that powders and capsules are not prescribed at the Michael Reese Hospital as much time can be saved by dispensing the same medicaments in liquid form. Large quantities of the fast-moving medicaments are prepared in the form of 100%, 50% and 25% solutions.

Mr. Gray mentioned the interesting point that at the Presbyterian Hospital a committee exists, the pharmacist being an important member of this committee, that meets and discusses the new preparations placed on the market as to merit and price. In all cases official and non-secret medicaments are used where possible.

Mr. Morrison, in the course of his discussion presented a comparison of the prices of manufactured products to those made by the hospital pharmacists. The resulting figures should be an incentive to all pharmacists to manufacture more of his official preparations.

Exceptions were cited where it is practically impossible for a pharmacist to manufacture some preparations, and would be cheaper also, to purchase from the large manufacturing concerns.

After a five-minute recess the meeting was again called to order and Mr. Morrison presented a series of incompatibilities that he had encountered at the hospital. Methods of overcoming these were shown and discussed.

LAWRENCE TEMPLETON, *Secretary.*

DETROIT.

The February meeting of the Detroit Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at Webster Hall, February 22nd. A special Washington Birthday dinner preceded the meeting and a large gathering turned out to hear Director Parr, which was augmented by the attendance of the members of the Board of Pharmacy.

Owing to the absence of President Felix Johnson, the meeting was called to order by Treasurer Fred Ingram. He introduced the University of Michigan alumni, including Clarence Weaver, Leonard A. Seltzer, Glenn Staines, N. M. Henry and Prof. C. C. Glover, and Norman A. Weess of Everett and V. C. Piaskowski, new members of the Board of Pharmacy.

The Colleges of Pharmacy were represented by Dean R. T. Lakey of Wayne University, Prof. R. L. Dorion of Detroit Institute of Technology, and Dr. Howard B. Lewis of the University of Michigan. Dr. Lewis confirmed his previous invitation to hold the May meeting of the Detroit Branch, in conjunction with the Pharmaceutical Conference of the College of Pharmacy of the University of Michigan on May 17, 1934.

S. R. Klegon represented the clerks. Mr. Ingram then introduced the speaker of the evening, another University of Michigan Alumnus, Director of Drugs and Drug Stores, E. J. Parr.

The director presented a very interesting picture of the many problems confronting pharmacy in Michigan. He said the retail druggist must have protection against outside interests that are making strong inroads on the legitimate drug business. He referred to the vendors particularly and the patent medicine stores. During the last thirty days 125 vendors were licensed by the State and 15 convictions obtained for vending without a license.

The Michigan Clinical Thermometer Law was referred to by Director Parr as needing amendment. He claimed Connecticut, Massachusetts and New York alone had satisfactory thermometer legislation.

Mr. Parr predicted the grading of drug stores in the near future into three classes—the professional, semi-professional and merchandising stores. He said standards must be set up for qualification and inspection to include equipment, scales, weights and pharmaceuticals carried in stock. The Board of Pharmacy can only do what the laws allow, therefore, the answer is with the pharmacist; the Board is empowered to make rulings but not laws.

The listeners were astounded to learn that about one thousand manufacturers of medicinal preparations by non-pharmacists were established in kitchens, barns, etc., in Michigan over which the Board has practically no control. A $20 license is required for every dog remedy; veterinary medicines are controlled by the State but no such control is exercised over medicines for humans. He pointed out that the drug laws in Michigan were very indefinite and offer very little protection to the druggist and even less to the public health. Improvement of the pharmacy laws which are unjust to the future generation was urged. The Board of Pharmacy desires to have qualified pharmacists; within the last month three drug store licenses were revoked for not operating according to the law. The Board at all times must consider the public health.

The pharmacists were informed that on July 1, 1934, new numbers were to be issued to drug stores in order to give an accurate check on the number of stores operating in Michigan. At present 5500 licenses have been issued with less than one-half of that number active.

A general discussion followed, led by Dean R. T. Lakey.

On motion of Prof. C. C. Glover, a rising vote of thanks was given to Director Parr for his enlightening and interesting talk, which brought a most profitable and pleasant evening to a close.

BERNARD A. BIALK, *Secretary.*

UNIVERSITY OF FLORIDA STUDENT BRANCH.

The March meeting of the University of Florida Student Branch was called to order at 5:10 P.M., March 21st, by President Jones.

A discussion of the action to be taken by the Local Branch on a design for appropriate insignia was participated in by members Coniglio, McLean and Johnson. The matter was deferred until such time as all other Student branches had answered requests for opinions.

There being no further business, President Jones called for nominations for officers for the coming year. The following were nominated:

For *President*, Frank L. Coniglio

For *Vice-President*, Arthur Goldstein, Robert L. White

For *Secretary*, Richard S. Johnson

For *Treasurer*, Paul Fehder, Dale Roth.

On voting (by secret ballot) Messrs. White and Fehder were elected to the offices of *Vice-President* and *Treasurer*, respectively. There being only one nomination for each of the other offices the secretary was instructed to cast a ballot for Messrs. Coniglio and Johnson for the offices of *President* and *Secretary*.

After appropriate remarks by retiring President Jones and President-Elect Coniglio the meeting was adjourned.

FRANK S. CONIGLIO, *Secretary.*

NEW YORK.

The March meeting of the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on March 12th, in the College of Pharmacy, Columbia University. About one hundred members and their guests attended.

President Ballard was in charge of the meeting. After the meeting was called to order, the report of the secretary was read and accepted.

Chairman Kassner, of the Professional Relations Committee then announced the Physicians and Pharmacists' Meeting to be held on March 29th in the Academy of Medicine under the auspices of the Academy of Pharmacy. Every one present was urged to attend.

Chairman Dauer of the Committee on the Progress of Pharmacy then reported on the following new remedies:

Mercupurin—an organic compound of a mercurial salt and theophylline. It is used in cardiac edema, cardiorenal edema and for cirrhosis of the liver. It is a powerful diuretic.

Pentnucleotide—a mixture of the sodium salts of pentose nucleotides. It is used in cases of agranulocytic angina.

Novatropin—methylhomatropine bromide. Its paralytic action is comparable to that of atropine and it is eight to ten times as potent as homatropine. However, it is less than one-thirtieth as toxic as atropine.

President Ballard presented the guest speaker for the evening, Dr. Ernst Boas, who discussed "The Heart and Its Diseases."

Dr. Boas began by giving some very interesting statistics on heart diseases. He showed that the death rate from heart diseases was gradually mounting, but that in some age classes decreases were to be noted. However, improved methods for diagnosis made comparison of recent figures with old rather unreliable; for, not many years ago, heart disease diagnosis had not reached a point comparable with methods employed to-day.

Having briefly reviewed the mortality statistics Dr. Boas went on to discuss the causes of heart diseases. These he grouped into four classes.

1. Rheumatism
2. Syphilis
3. High blood pressure
4. Arterio sclerosis.

The latter two go hand in hand, making really but three causes. After emphasizing that methods for preventing heart diseases were unknown, Dr. Boas went on to discuss progress made in controlling the diseases which lead to heart afflictions. For younger persons, rheumatic fever, is a primary cause of heart disease. By reducing the prevalence of this disease some progress in conquering heart disease has been made.

The speaker went further to explain that a definite type or kind of heart disease develops from rheumatic fever, and that every fresh attack of the disease causes new heart damage.

About five to ten per cent of the adult cases of heart disease can be traced to syphilis. This disease can now be controlled and hence, heart disease from this cause can be controlled. However, heart damage usually has already taken place by the time a diagnosis is made. The heart damage is usually upon the valves of the aorta.

High blood pressure is important as a cause of heart disease. It generally runs in families, and is probably due to some disturbance in the flow of internal secretions. The heart must work harder under such circumstances and it gradually enlarges and weakens. This usually requires many years and heart failure finally results.

Arterio sclerosis is a sign of senility. It usually occurs in persons after forty. It may bring on apoplexy, or the kidneys may fail. Arterio sclerosis picks out the vital organs for its attack.

Dr. Boas then showed numerous slides which illustrated many points covered in his talk thus far. He also showed some extremely interesting graphs made with an electrocardiogram and explained fully what use the specialist made of this information to aid him in his diagnosis.

In his concluding remarks the speaker made clear that there are heart diseases, specific afflictions of the heart, and that a single expression to describe all of these was misleading. He again pointed out the diseases which precede heart diseases and discussed their control as far as possible. In treating heart diseases many new remedies are being tried. Digitalis is, of course, a standard. But quinidine is being used in some types with marked success. Many mercurial organics are being used for their diuretic properties, and large doses of urea and ammonium chloride are also used for the purpose.

Finally, Dr. Boas repeated that we do not know how to prevent heart diseases but that this subject was receiving very considerable attention and much study was under way.

After answering several questions a rising vote of thanks was accorded Dr. Boas for his highly informative discussion.

RUDOLF O. HAUCK, *Secretary*.

NORTHERN NEW JERSEY BRANCH.

The March meeting of the Northern New Jersey Branch was convened at the Rutgers University College of Pharmacy on March 19th, by President Little.

Plans for the April meeting, at which time we will have the pleasure of entertaining the physicians of this neighborhood, were discussed. Professor Schicks in detailing the arrangements for the evening explained that the only ticket of admission required of the pharmacists who attend will be that they are accompanied by one or more medical friends.

The program is to be made up mostly of demonstrations illustrating the compounding of type prescriptions, the use of new apparatus in prescription work, and the manufacturing of galenical preparations. The Rutgers University College of Pharmacy is turning over its laboratory facilities and staff for this work.

In addition to the practical laboratory demonstrations, the Hudson County and Elizabeth Pharmaceutical Associations will have exhibits which display the work of the prescription room to excellent advantage. Parke, Davis and Company and Eli Lilly Company are also coöperating with displays of glandular products.

The Nominating Committee reported the names of the following candidates for officers of the Branch for the ensuing year: *Honorary President*, Philemon E. Hommell; *President*,

Ernest Little; *Vice-President*, G. C. Schicks; *Secretary*, L. W. Rising, and *Treasurer*, A. F. Marquier. The candidates were elected by unanimous ballot.

Professor O. P. M. Canis gave a short talk on the rapid return of Pharmacy to botanical materia medica. He felt that the trend was very definitely in that direction and in order to profit by it pharmacists should begin an intensive study of the U. S. P. and N. F. herbs. Drawing many illustrations from his forty-five years' experience as a retail pharmacist he vividly portrayed the potentialities of this swing in prescription writing.

To complete our evening of professional discussions Professor C. L. Cox presented a talk on emulsions. The theoretical considerations were nicely balanced with the practical manufacturing problems arising both in the making of emulsions, and the preventing of their formation at times when their presence would disrupt certain processes. By means of laboratory demonstrations made while he talked Professor Cox forcibly illustrated many oddities in emulsion making, and the use of different types of equipment.

L. W. RISING, *Secretary*.

NORTHERN OHIO.

A joint meeting of the Northern Ohio Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION and the Western Reserve University Student Branch, A. PH. A., was held in the Faculty Club of Western Reserve University, Cleveland, Ohio, April 13, 1934. The meeting was under the auspices of the Student Branch and was preceded by a dinner, the guest of honor being Secretary M. N. Ford, of the Ohio State Board of Pharmacy and secretary-treasurer of the Conference of Pharmaceutical Law Enforcement Officials.

After the dinner, the meeting adjourned to the class-room auditorium of the School of Pharmacy where the membership and others interested in Pharmacy listened to a very much worth-while and interesting talk on Mr. Ford's experiences, covering a period of more then twenty years, as secretary of the Ohio Board of Pharmacy and as an enforcement officer of Pharmacy laws.

Some Court decisions were reviewed and some episodes touched upon in order to demonstrate the fact that the path of a law enforcement official in fields of professional practice is not a rosy one. However, it was pointed out, there seems to be a gradual improvement all along the line in Ohio and other states of the nation due, largely, to the concerted efforts of the members of the Pharmaceutical Law Enforcement Conference.

Mr. Ford congratulated the Student Branch on its manifested interest in better pharmacy and assured the members that the future of professional pharmacy and its ethical practice will be influenced in no small degree by groups similar to those that composed this joint meeting.

Just previous to the dinner meeting the Council of the Northern Ohio Branch, A. PH. A., in addition to some routine business matters adopted the following resolution:

RESOLUTION ON THE DEATH OF HERBERT E. BENFIELD.

WHEREAS, Our highly respected and much beloved co-worker, Herbert E. Benfield, passed away on February 26, 1934, and,

WHEREAS, Mr. Benfield was one of the founders of this organization and held its ideals and purposes in the highest esteem, and,

WHEREAS, His exemplary service as president and committeeman, along with his regular attendance when not in office amply demonstrated his willingness to make more than lip contributions, and,

WHEREAS, His exceptional friendliness and genial fellowship, his kindliness and toleration won the admiration and endearment of all his associates.

Resolved, that we express our deep sorrow at his death and extend to his widow and relatives our heartfelt sympathy in their hour of bereavement.

Resolved, that a copy of this resolution be sent to Mrs. Benfield, be entered in our minutes and be sent to the Editor of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

N. T. CHAMBERLIN, *Secretary*.

PHILADELPHIA.

The March meeting of the Philadelphia Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held in the auditorium of the Philadelphia College of Pharmacy and Science, on Tuesday evening, March 20th.

The occasion was that of the annual dinner tendered by the members of the branch to its past-presidents in honor of their loyalty to the organization.

The following past-presidents attended, and each was called upon by President Eby for a word of greeting and a few appropriate remarks: W. A. Pearson, E. Fullerton Cook, Ambrose Hunsberger, W. W. McNeary, Brua C. Goodhart, Raymond Hendrickson, Adley B. Nichols, James C. Munch and William J. Stoneback. Although topics were not assigned these speakers, the general trend of their discussion concerned the necessity for advancing the pharmaceutical profession with an outlook toward its future. Favorable legislation to abolish unsatisfactory conditions, coöperation with other similar professions, the need for a social survey for pharmacy and for increased pharmaceutical research were among the suggestions offered by the various past-presidents.

An illustrated talk on "The Appreciation of Art" by Mr. V. McCormick was then enjoyably received by the group.

Near the close of the meeting the annual reports of the secretary and treasurer were read and approved, and the chairman of the Nominating Committee presented a list of officers for the coming year. The following were unanimously chosen:

President, Alfred Barol
First Vice-President, Theo. A. Campbell, Jr.
Second Vice-President, L. L. Miller
Secretary-Treasurer, Edmund H. MacLaughlin.

President Eby thanked the members assembled for their coöperation during his term of office and after installation of the new officers the meeting was adjourned.

EDMUND H. MACLAUGHLIN, *Secretary.*

NORTHWEST PHARMACEUTICAL BUREAU ELECTS OFFICERS.

The following officers were elected: *President*, J. P. Jelinek, St. Paul; *Vice-Presidents:* J. J. Gillespie, Des Moines and John Heerema, Pella, Iowa; *Treasurer*, Robert M. Gibson, Des Moines, Iowa; *Secretary*, Rowland Jones, Gettysburg, South Dakota; *Advisory Secretary*, Frank M. McCabe, St. Paul. *Executive Committee:* N. Vere Sanders, Albert Lea, Minnesota; P. J. Jepson, Newton, Iowa; John Veenker, Northwood, Iowa, and W. F. Sudro, Fargo, North Dakota.

OKLAHOMA CITY EMPLOYS PHARMACIST.

After quite a discussion of the Oklahoma City officials with the State Board of Pharmacy, Oklahoma City has decided to employ a registered pharmacist and Frank Weaver has been named as pharmacist. There was quite a contention over the matter, the city attorney having ruled that Oklahoma City was within its rights in dispensing drugs without a pharmacist.

FOUR NEW VETERANS' HOSPITALS TO BE OPENED.

Four new veterans' hospitals with an aggregate capacity of 963 beds, built at a cost of $3,002,014, are to be placed in commission as a result of liberalization of the veterans' relief regulations promulgated under the Economy Act of 1933. The institutions are in Batavia, N. Y., Cheyenne, Wyo., Des Moines, Iowa, and Fayetteville, Ark. Two other hospitals are under construction, a general hospital at San Francisco, and one for nervous and mental diseases at Roanoke, Va.

THE WEIGHTS AND MEASURES LAW IN CHINA.

The Commercial Counsellor at Shanghai reports that no detailed regulations have yet been issued for the Weights and Measures Law. It is understood, however, that invoices should be made out in conformity with the metric system and, in order to avoid confusion, goods should also be marked according to that system. The units to be employed for this purpose are those of the international metric standard and not the Chinese adaptations thereof.

EDITORIAL NOTES

The *New York Times* of April 15th, in commenting on the congratulations of Lord Rutherford to Drs. Urey, Brickwedde and Murphy on the discovery of double-weight-hydrogen, expresses appreciation also because of the conspicuous part that Americans have played in physical research during the last two decades.

The editorial concludes: "In an era when the United States is looked upon abroad as the land of materialism, the place where only the profit-making motive counts, it is good to read Lord Rutherford's words and to realize that not only the spirit of scientific research, but the ability to carry on the work of the great, lies within our laboratories."

Some of the processes of pharmacy may become subjects of research in connection with the important discovery.

QUALITY OR QUANTITY?

The *Oil, Paint and Drug Reporter* of April 9th, comments on a recent decision that "Many men will be of many minds with respect to a dictum of a United States Circuit Court of Appeals judge in a recent decision having to do with the regulation of business; for the opinion expressed clashes with many theories and with many views developed beyond the theoretical stage. In fact, the judge's utterance is at variance with certain economic delineations set forth in the statutes of the United States and of a number of the States. There are those who will find in the dictum disagreement with certain points of the popular conception of constitutional grants of individual rights."

Here is what the appellate jurist said:

Surely, it is a mild assumption that the more vital interest in the end may demand that there be less goods sold at higher prices rather than that all existing manufacturers should remain in business. He would be a hardy exponent of noninterference who should assert the opposite to-day, if for instance, the rise in cost was due to improvement in working conditions, or in the hygienic quality of the product.

"DRUGGED FOODS."

The *Journal of the American Medical Association* states that "Medicating common food articles with drugs—such as the addition of phenolphthalein to chewing gum, acetylsalicylic acid to candy, and senna to bread—is becoming a growing menace, and must be viewed with apprehension and concern as a danger to public health. The general appearance of these drugged foods does not distinguish them from the respective non-drugged forms; label declaration of the added drugs cannot be expected to prevent their fortuitous misuse or their consumption by the uninformed, the unobservant or those unable to recognize the significance of label statements. There is, therefore, the ever-present likelihood that children, and even adults, may unsuspectingly or ignorantly consume such drugged foods with results that may be disastrous."

DEFINITION OF POISON.

Dr. John J. Abel, retiring president of the American Association for the Advancement of Science, in his recent Boston address, said "there is no definition of a poison in medical law of the United States or England. No one has ever been able to give a concise and accurate definition of a poison that would apply to every one of the many thousands of known poisons." Dr. Abel made this statement to emphasize how obscure is man's knowledge of poisons and how meaningless is the term in a basic sense. "Nature," he said, "has not affixed a poison label to any particular substance or class of substance. The pharmacist does that." Whether a drug is poisonous or not depends on its use or the amount taken.

REVISION OF BRITISH PHARMACEUTICAL CODEX.

Under the direction of the Council of the Pharmaceutical Society of Great Britain, reports are being issued preliminary to revising sections of the British Pharmaceutical Codex. The report of the pharmacy sub-committee presents a summary of the principal new or revised formulas recommended by it for inclusion in the British Pharmaceutical Codex of 1934. The sub-committee recommends the inclusion of formulas for a number of preparations from earlier pharmacopœias which are not included in the British Pharmacopœia of 1932 but are still in more or less frequent demand. Useful comments on the proposed formulas will be appreciated by the editor, C. E. Corfield, 17 Bloomsbury Square, London, W. C. 1, England.

PERSONAL AND NEWS ITEMS.

Dr. Frank A. Delgado has been appointed Administration Member of the National Drug Code Authority.

Lester E. Bishop, of Laurens, S. C., has been named associate editor of the *Southeastern Drug Journal.* He is president of South Carolina Pharmaceutical Association and member of South Carolina Board of Pharmacy.

Dr. John J. Abel was awarded the Kober medal for 1934 for scientific research; in 1928, he was awarded the gold medal of the London Society of Apothecaries.

Our senior ex-president **John Uri Lloyd** celebrated his 85th birthday, April 19th; he has been a member of the ASSOCIATION since 1870, and served as president 1887–1888.

Our fellow-member **Hugo Kantrowitz** celebrated his 80th birthday on April 8th.

Prof. Charles W. Greene, professor of physiology and pharmacology at the University of Missouri, was elected president of the American Physiological Society at the New York meeting.

William F. Smith, pharmacist in Perth Amboy, N. J., and graduate of New Jersey Law School, has been appointed special Assistant U. S. District Attorney for New Jersey.

President C. Thurston, of the National Association of Boards of Pharmacy, has been commissioned a Colonel by Governor Ruby Lafoon of Kentucky.

Prof. Gustav Bachman, Minnesota Pharmaceutical Association, has declined reëlection as secretary for the term beginning February 1935, at which time he will be succeeded by A. Roy F. Johnson, *executive secretary.* C. V. Netz will continue as *acting secretary* until February 1935. He will serve as field secretary during the summer months. Professor Bachman sustained serious injuries in an automobile accident some time ago.

Wroe Alderson has resigned as assistant chief of the domestic division of the U. S. Bureau of Foreign and Domestic Commerce. He is now director of a Research Bureau, New York, organized for research activities for manufacturers, distributors and trade associations.

William H. Johnson, who has been acting as executive secretary of the National Retail Drug Code Authority since its organization, has resigned that position and has been succeeded by Paul Pearson, Washington, who has taken over Mr. Johnson's duties with title of assistant secretary. Mr. Pearson for twenty-four years has been president of the Washington Wholesale Drug Exchange and is president of the District of Columbia Pharmaceutical Association.

D. D. Adams, after long years of service, has retired as treasurer of Nebraska Pharmaceutical Association.

P. O. Bugge, Bisbee, No. Dak., noting the article in the A. PH. A. JOURNAL on Henrik Ibsen, referred to his winning a national prize, in 1927, for his poem on Henrik Ibsen, presented in a contest at the time of the Ibsen centennial celebration in Minneapolis.

Charles Morgan, of Morgan & Millard, Baltimore, states that while gain in business volume is not large, the trend is toward pharmaceuticals.

A PRICE LIST TO BE COMPILED.

The Retail Drug Code Authority in conference, on April 18th, acted upon the suggestion that there should be compiled a price list for drug products, which could be used as the official price list in the interpretation of "cost" under Section 6 of the Retail Drug Code. These prices are based on the "manufacturer's wholesale list price per dozen" and will include all discounts, free goods, etc., as defined in the recent amendment to the Retail Drug Code.

A preliminary list of 400 items will be compiled, and to this will be added all items essentially necessary for the use of the various code authorities. Corrections to the list will be made, immediately upon the issuance of any new price list by the manufacturer.

PRICE REGULATION FOR RETAIL DRUG TRADE.

The National Recovery Administration, on April 19th, announced issuance of an order under which a drug retailer may reduce his price to meet the price of a competitor until such time as the National Retail Drug Code Authority, or the Local Authority, shall have announced a price which shall be *prima facie* evidence of the correct price.

Upon announcement of this *prima facie* correct price by the Code Authority, the new order provides that reductions below such announced price shall constitute a violation of the code unless the retailer is able to prove that the correct price is lower than that announced by the Code Authority.

The new order becomes effective immediately.

OBITUARY.

FLORIN J. AMRHEIN.

Florin J. Amrhein, Assistant Professor of Chemistry at Massachusetts College of Pharmacy and member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1916, died March 30th. He had been in poor health for several months and was to undergo a surgical operation on March 31st. The deceased was born in Boston, August 3, 1892, the son of John and Catherine (Luzio) Amrhein.

Professor Amrhein graduated from the Boston Latin School, Boston University, and from Massachusetts College of Pharmacy in 1915; he also studied at Massachusetts Institute of Technology. Soon after graduating from the Massachusetts College of Pharmacy he was elected a member of its faculty.

Professor Amrhein was *Grand Regent* of Kappa Psi. The deceased is survived by his widow, Dr. Elizabeth McCarty Amrhein, and a son, Florin, Jr., to whom sympathy is expressed.

The news of Professor Amrhein came as a shock, as the writer had been in correspondence with him during the week before his passing; a paper by him is printed in the March issue of the JOURNAL. In recent years he had been interested in Vitamin D research.

H. E. BENFIELD.

Herbert E. Benfield, member of the AMERICAN PHARMACEUTICAL ASSOCIATION and pharmacist of Cleveland, Ohio, died February 26th, following a heart attack. At the time of his death, Mr. Benfield conducted two pharmacies in Cleveland. He was active in organization work and highly esteemed by his co-workers and patrons. The deceased is survived by his widow and a brother, C. W. Benfield, pharmacist of Solon, Ohio.

EUSTACE H. GANE.

Eustace H. Gane, member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1895, died at his home in Montclair, N. J., March 23rd, aged 64 years. For twenty-five years, prior to establishing the firm of manufacturing chemists of Gane & Ingram, in 1923, he was associated with McKesson & Robbins. At the time of his passing Mr. Gane was in the midst of plans for further expansion of the business he had founded and successfully conducted. Mr. Gane was well and favorably known and a frequent contributor to the Scientific Section of the ASSOCIATION, and gave freely of his knowledge to those who came to him for advice. He held membership in the Chemist Club and Drug and Chemical Division of New York Board of Trade.

HARVEY H. ROBINSON.

Harvey H. Robinson, member of the AMERICAN PHARMACEUTICAL ASSOCIATION, president of the Henry B. Gilpin Company, wholesale druggist, Baltimore, died March 30th, after a brief illness, aged 62 years.

After completing a business course in Baltimore, he entered the employ of Gilpin Longdon & Company as a clerk. When the company reorganized as the Henry B. Gilpin Company, Mr. Robinson became treasurer; in 1910, he became vice-president and general manager and, in 1916, he was made president.

Mr. Robinson was interested in civic and social activities, resulting in Boys' Brigade predecessor of the Boy Scouts; he served as chairman of the Baltimore committee on public athletics and community work. He was active in the work of the national drug trade bodies and in all movements designed to benefit the trade: He served as president of the Baltimore Drug Exchange; as a member of the board of control and as vice-president and on various N. W. D. A. committees. In the work of the latter to formulate and adopt an NRA code, he was one of the foremost workers. Mr. Robinson held membership in the Masonic bodies, the Baltimore Merchants Club and the Rolling Road Golf Club. He is survived by his wife, Mrs. Edna Sarah Robinson; two daughters, Misses Mazie E. and Rebekah O. Robinson; his mother, Mrs. Elizabeth A. Robinson; a brother, John O. Robinson, and a sister, Mrs. Walter Lee Simmons.

FRANK B. STEPHENS.

Frank B. Stephens, member of the AMERICAN PHARMACEUTICAL ASSOCIATION and a former president of Florida Pharmaceutical Association, died at a St. Augustine hospital after a brief illness, aged 65 years. He was an honor graduate of the University of Chicago and before coming to St. Augustine operated three drug stores in Toledo, Ohio.

Mr. Stephens had been engaged in pharmacy at St. Augustine for 28 years and was one of the most active workers in Florida pharmacy. He was a member of the Masonic bodies. His widow, a brother and a sister survive him.

WALTER B. SWINDELL.

Walter B. Swindell, president of the Swindell Brothers Glass Company, died at his home in Baltimore following a heart attack. The deceased was born in Baltimore in 1850, and with his father, the late William Swindell, founded the glass company of which he was head, in 1869. A brother, Charles J. B. Swindell; a son, Walter B. Swindell, Jr., and three daughters survive the deceased.

DR. J. F. SCHAMBERG.

Dr. Jay Frank Schamberg, professor of dermatology at the medical school of the University of Pennsylvania, Philadelphia, and widely known as one of the co-producers in the United States of synthetic salvarsan during the war when supplies of the product were cut off from Germany, died March 30th at his home in Philadelphia, aged 63 years. He was a graduate of the Medical Department of the University of Pennsylvania in 1892, and continued his studies in Europe and then practiced in Philadelphia, specializing in dermatology and syphilology. With Drs. George W. Raiziss and Dr. John A. Kolmer, he succeeded in manufacturing salvarsan, in the United States and the $750,000 profits resulting therefrom were donated to the Research Institute of Cutaneous Medicine. Dr. Schamberg is survived by his wife and two children.

Alfons Adolph, who invented view post cards, died in Passau, Germany, March 28th, aged 80 years. With a special press he printed the first card in 1879 and it was followed by world-wide popularity.

SOCIETIES AND COLLEGES.

ANNOUNCEMENT BY CHAIRMAN BRADLEY OF THE COMMITTEE ON TRANSPORTATION.

The Identification Certificate Privilege has been secured from the various railroad passenger associations for the 1934 meeting in Washington. This entitles the members to buy tickets for themselves and dependent members of their families, on certificates sent out by Secretary Kelly, for one and one-third fare for the round trip, going and returning by the same route or by diverse routes.

The following regulations governing the sale and use of these tickets have been received from the Central Passenger Association and similar regulations apply to the sale and use of tickets from points in the territories of other passenger associations.

(*a*) Round-trip tickets at one and one-third fare (with minimum of $1) for the round trip, on Identification Certificates, good *via* same route in both directions, will be sold from the above-mentioned territory from April 28th to May 9th, inclusive, and before being honored for return passage, return portions thereof must be validated (in space provided therefor) at Washington, D. C., or Baltimore, Md., by ticket agents' dating stamp at the regular ticket offices of the lines over which tickets read into Washington, D. C., or Baltimore, Md., from April 30, 1934, to and including thirty days in addition to date of sale, and when validated, tickets will be good for return, leaving on any day within final limit; passenger must, however, reach original starting point within transit limit shown on ticket.

(*b*) For tickets *via* diverse routes: Round-trip tickets will also be sold on the one and one-third fare basis, going *via* any authorized route published in one-way tariffs, returning *via* any other authorized route published in one-way tariffs, the round-trip fare being computed by using one-half of the round-trip fare (that is, half of the $1^1/_3$ fare) from starting point to destination applying *via* route used on the going trip, plus one-half of the round-trip fare (that is, half of the $1^1/_3$ fare) from starting point to destination applying *via* route used on the return trip. Return portions of tickets must be validated at destination by ticket agents' dating stamp at regular ticket offices of lines over which tickets read returning from place of meeting to original starting point. Return limit 30 days in addition to date of sale: selling dates and other conditions to be the same as will apply in connection with tickets issued *via* same route in both directions (Item "a").

Children of 5 and under 12 years of age when accompanied by parent or guardian will, under like conditions, be charged one-half of the fare for adults.

It will be necessary for members, when purchasing round-trip tickets, to present and surrender the Identification Certificate issued account of your meeting and to indicate to ticket agents which ticket is desired—namely:

(1) One and one-third fare for round trip,

good *via* same route in both directions, final return limit 30 days in addition to date of sale.

(2) One and one-third fare for round trip, going *via* any authorized route and returning *via* another authorized route, final return limit 30 days in addition to date of sale.

PAPERS FOR ALL A. PH. A. SECTIONS AND CONFERENCES.

Contributors of papers should send their papers to the Section and Conference Officers, promptly. If the papers are not ready send in the titles, also abstracts of the papers.

Officers of the Sections and Conferences are printed in the March issue of the JOURNAL, pages 278 and 279.

Programs of the Sections will be printed in the Official Program.

TENTATIVE GENERAL PROGRAM FOR THE EIGHTY-SECOND ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION AND RELATED ORGANIZATIONS, HOTEL SHOREHAM, WASHINGTON, D. C., MAY 7–12, 1934.

All dates included in special fare arrangements with railroads.

MAY 6–7.

Plant Science Seminar. Program and Meeting Rooms to be arranged. A field trip will be arranged for Sunday, May 6th.

SATURDAY, MAY 5.

National Conference on Pharmaceutical Research—Club Room. Meetings at 2:00 P.M. and 8:00 P.M.

Dinner between afternoon and evening sessions at Hotel Shoreham.

SUNDAY, MAY 6.

American Council on Pharmaceutical Education—Time and Place to be arranged.

MONDAY, MAY 7.

9:00 A.M. Council A. PH. A.—Conference Room.
9:00 A.M. N. A. B. P.—Main Ball Room.
9:00 A.M. A. A. C. P.—Executive Committee—Garbo Room.
9:00 A.M. Teachers' Conferences, A. A. C. P. Chemistry Conference—Club Room.
Pharmacy Conference—Grill Room.
Materia Medica Conference—Empire Room.
Pharmaceutical Economics Conference—Card Room.
1:30 P.M. N. A. B. P.—Main Ball Room.
1:30 P.M. A. A. C. P.—Club Room.
6:00 P.M. Dinner, N. A. B. P.—The Kennedy-Warren.
6:00 P.M. Dinner, A. A. C. P.—The Kennedy-Warren.
8:00 P.M. N. A. B. P.—West Ball Room.
8:00 P.M. A. A. C. P.—Club Room.
9:30 P.M. Reception—(Informal) followed by dancing.

TUESDAY, MAY 8.

9:00 A.M. Joint Meeting N. A. B. P. and A. A. C. P.—West Ball Room.
1:30 P.M. First Session, House of Delegates—West Ball Room.
2:30 P.M. N. A. B. P.—West Ball Room.
2:30 P.M. A. A. C. P.—Club Room.
6:30 P.M. Banquet, A. PH. A. and Related Organizations—Main Ball Room.

WEDNESDAY, MAY 9.

10:00 A.M. Dedication of the American Institute of Pharmacy—at the Building—2215 Constitution Avenue.
12:30 P.M. Luncheon, Recipe Book Committee.
2:00 P.M. First Session, Scientific Section—West Ball Room.
2:00 P.M. First Session, Section on Education and Legislation—Empire Room.
2:00 P.M. First Session, Section on Commercial Interests—Club Room.
2:00 P.M. First Session, Conference of Pharmaceutical Association Secretaries—Card Room.
6:00 P.M. Dinner, Kappa Psi Fraternity.
6:00 P.M. Dinner, Phi Delta Chi Fraternity.
6:00 P.M. Dinner, Rho Chi Fraternity, followed by annual convention.
8:00 P.M. Second Session, House of Delegates—Club Room.

THURSDAY, MAY 10.

9:00 A.M. Council A. PH. A.—Conference Room.
9:00 A.M. Second Session, Section on Commercial Interests—Club Room.
9:00 A.M. Second Session, Scientific Section—West Ball Room.
9:00 A.M. First Session, Section on Practical Pharmacy—Empire Room.

9:00 A.M. First Session, Section on Historical Pharmacy—Card Room.

9:00 A.M. First Session, Conference of Law Enforcement Officials—Garbo Room.

12:00 M. Veteran Druggists' Luncheon.

2:00 P.M. Second General Session, A. PH. A.—West Ball Room. This session will be a continuation of the dedication exercises of the American Institute of Pharmacy and will be devoted to a general discussion of future plans and of the work to be carried on in the Institute.

6:00 P.M. Dinner, Lambda Kappa Sigma Sorority—The Kennedy-Warren.

8:00 P.M. Joint Session, Scientific Section and Section on Practical Pharmacy and Dispensing—West Ball Room.

8:00 P.M. Joint Session, Section on Education and Legislation, Conference of Pharmaceutical Law Enforcement Officials and Conference of Pharmaceutical Association Secretaries—Club Room.

FRIDAY, MAY 11.

9:00 A.M. Third Session, House of Delegates—West Ball Room.

2:00 P.M. Third Session, Scientific Section—West Ball Room.

2:00 P.M. Second Session, Section on Historical Pharmacy—Main Ball Room.

2:00 P.M. Second Session, Section on Practical Pharmacy—Empire Room.

2:00 P.M. Second Session, Section on Education and Legislation—Club Room.

2:00 P.M. Second Session, Conference of Law Enforcement Officials—Garbo Room.

2:00 P.M. Second Session, Conference of Pharmaceutical Association Secretaries—Card Room.

5:45 P.M. Dinner, Former Presidents A. PH. A.—The Kennedy-Warren.

6:00 P.M. Special dinners.

7:30 P.M. Final Session, House of Delegates—West Ball Room.

8:30 P.M. Final General Session—West Ball Room.

10:00 P.M. Farewell Party.

10:00 P.M. Council A. PH. A.—Conference Room.

SATURDAY, MAY 12.

9:15 A.M. Automobile Trip through Washington and to Mt. Vernon, Alexandria and Arlington. Busses will leave from the Shoreham Hotel.

SCIENTIFIC SECTION.

The 82nd annual meeting will be held in Washington, D. C., during the week of May 7th, and will include the dedication of the new headquarters building. The Scientific Section plans to hold several interesting sessions but in order to accomplish this the officers must have your coöperation.

Since the Convention date is much earlier than usual, it will be necessary for authors of papers to submit titles and very short abstracts to the secretary promptly in order that the titles may appear in the printed program. Authors should indicate whether the papers are to be presented in person or by title and should bear in mind that ten minutes is the time limit for the presentation of a paper.

L. W. ROWE, *Secretary*, Scientific Section, c/o Parke, Davis & Co., Detroit, Michigan.

F. E. BIBBINS, *Chairman*, Scientific Section.

SECTION ON HISTORICAL PHARMACY.

The forthcoming meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION will be an occasion of unusual interest because it will be held at *home*, in Washington, May 7th. That fact alone will be one of great historical significance to the ASSOCIATION and its friends.

This meeting should be one of the best for the Historical Section, and you are invited to present a paper upon some phase of historical pharmacy.

Papers that are submitted become permanent records in the archives of the ASSOCIATION.

Pictures and photographs greatly enhance the value of papers. The stories of men, institutions and associations of pharmacy are always interesting. Send us the *titles and abstracts* of your stories at your earliest convenience.

We are all making pharmacy history. Let's record it.

C. O. LEE, *Secretary*, Purdue University, Lafayette, Ind.

Programs of all Sections are developing nicely.

PROGRAM, LAW ENFORCEMENT OFFICIALS.

1. Call to Order.
2. Remarks of Chairman, Robert L. Swain.
3. Report of Secretary, M. N. Ford.
4. Report of Finance Committee.

ADDRESSES.

"The Place of the Attorney General in the Legislative and Law Enforcement Program, Hon. Herbert Levy, of the Maryland Bar."

"Is Pharmaceutical Legislation Best Served by a Pharmacist Member of the Legislature?, Frank C. Purdum, Pharmacist Member of the Maryland Legislature and Harry E. Bischoff, Pharmacist Member of the New Jersey Legislature."

"The Public Health Council of Kansas and the Value of Its Principles to the Pharmaceutical Program, W. Mac Childs, *Secretary*, Kansas Board of Pharmacy."

"The Place of the Control Laboratory in the Enforcement of the Food and Drugs Act, William F. Reindollar, Bureau of Chemistry, Maryland State Department of Health."

"Report of Special Committee to Define the Terms, 'Patent Medicine' and 'Proprietary Medicine,' A. L. I. Winne, Virginia, *Chairman*."

"The Enforcement of State Poison Laws, George W. Mather, *Secretary*, New York Board of Pharmacy."

"Coöperation between Federal and State Officials in the Enforcement of the Food and Drug Acts, W. S. Frisbis, United States Department of Agriculture."

"Informal discussion of enforcement procedure, inspection technic, legislative and other matters of special interest to the Conference."

TOPICS FOR ROUND TABLE DISCUSSION, CONFERENCE OF PHARMACEUTICAL ASSOCIATION SECRETARIES.

"Is it desirable, if so is it possible to form a National Association from the various State Associations with every member of the State Association automatically a member of the National Association without payment of additional membership dues?"

Discussion opened by A. L. I. Winne, secretary, Virginia Pharmaceutical Association.

"Is a State Drug Code desirable in addition to the National Code?"

Discussion opened by Prescott R. Loveland, secretary, N. J. Pharmaceutical Association.

"Since the State Associations have been ignored in the National Drug Code set-up, what should be the attitude of the State Associations to Code matters?"

Discussion opened by J. Lester Hayman, secretary, West Virginia Pharmaceutical Association.

"Can a plan be evolved whereby one membership fee can be made to cover State and National Association dues?"

Discussion opened by R. A. Turrel, secretary, Michigan State Pharmaceutical Association.

"The organization of Congressional Districts or County Units."

Discussion opened by J. W. Slocum, secretary, Iowa Pharmaceutical Association.

"Is the handling of liquor in drug stores under prohibition repeal on a satisfactory basis? What changes or improvements should be made?"

Discussion opened by F. V. McCullough, secretary, Indiana Pharmaceutical Association.

"Is it desirable, if so is it possible to have this Conference submit to each State Association each year some suggestions as to the program with the idea of unifying our efforts toward some definitive objectives, National in scope?"

Discussion opened by W. D. Adams, secretary, Texas Pharmaceutical Association.

"Is there a desirability and a possibility of holding joint meetings of the Pharmaceutical Associations with the State Medical and Dental Associations?"

Discussion opened by E. F. Kelly, secretary, Maryland Pharmaceutical Association.

"What steps can be taken through Association channels to curb the practise of manufacturers packaging 10¢ sizes of proprietary medicines and cosmetics for distribution through department stores?"

Discussion opened by Roy C. Reese, secretary, Kansas Pharmaceutical Association.

"To what extent can the professional phases of Pharmacy be made a part of our programs?"

Discussion opened by J. G. Beard, secretary, North Carolina Pharmaceutical Association.

PROGRAM OF NATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH, 1934 MEETING.

WASHINGTON, D. C., SATURDAY, MAY 5, HOTEL SHOREHAM.

First Session, 2:00 P.M.

1. Call to Order by Chairman.
2. Appointment of Nominating Committee.
3. Summary of Year's Activities and Outlook of Conference for the Future, by Chairman E. N. Gathercoal.
4. Reports of Officers.
   a. Report of Secretary.
   b. Report of Treasurer.
   c. Report of Executive Committee by Secretary.
5. Reports of Standing Committees.
   (1) Pharmaceutical Dispensing, W. J. Husa, *Chairman.*
   (2) Manufacturing Pharmacy, L. W. Rising, *Chairman.*
   (3) Medicinal Chemicals, George D. Beal, *Chairman.*
   (4) Pharmacognosy, H. W. Youngken, *Chairman.*
6. Roll Call of Delegates.
7. Adjournment for dinner. Arrangements will be made for a dinner for the delegates assembled.

An address pertinent to the work of the Conference will be delivered.

Dinner between afternoon ond evening sessions at Hotel Shoreham. Dr. Carl Voegtlin, Pharmacology Director of the National Institute of Health, will be the guest speaker.

Evening Session, 8:00 P.M.

8. (5) Pharmacology, J. C. Munch, *Chairman.*
   (6) Bacteriology, Immunology and Endocrinology, A. R. Bliss, *Chairman.*
   (7) Physical Chemistry, Arthur Osol, *Chairman.*
   (8) Educational Methods, A. B. Lemon, *Chairman.*
   (9) Pharmaceutical Economics, P. C. Olsen, *Chairman.*
   (10) Historical Pharmacy, C. H. LaWall, *Chairman.*
9. Reports of Other Special Committees.
   (1) Fellowship Award, J. C. Krantz, Jr., *Chairman.*
   (2) Publications, E. N. Gathercoal, *Chairman.*
   (3) Census of Research, J. C. Munch, *Chairman.*
10. General Discussion of the Status of Pharmaceutical Research.
11. Election and Installation of Officers.
12. Adjournment.

ROCKEFELLER INSTITUTE OF PUBLIC HEALTH IN JAPAN.

A Rockefeller Institute of Public Health, attached to the Tokyo Imperial University has been arranged for. It is expected that the proposed construction of the buildings will take two years. A hospital will be built in Kyobashi-ku, Tokyo, for the actual training of the students, and another local hospital will be built at Tokorozawa, Saitama Prefecture. Both of these hospitals will be contributed to the prefectures in which they are located.

A. D. M. A. CONVENTION.

The American Drug Manufacturers' Association held their twenty-third annual meeting, April 17th to 19th, inclusive, at the Greenbrier Hotel, White Sulphur Springs, W. Va. An interesting program of the sectional meetings was carried out and several important addresses delivered at the business sessions, one by H. J. Anslinger, Commissioner of Narcotics, on "Newly Discovered Narcotic Drugs and Their Uses." The speaker at the annual banquet was Mrs. Ida Wright Bowman, for many years on the staff of current history lectures for the League for Political Education in New York. In past years she has studied international affairs abroad.

TEXAS WILL BE WELL REPRESENTED IN WASHINGTON.

The Texas Board of Pharmacy will attend the Washington meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION in a body. Officers of the State Association and other Texas pharmacists will be in the party; an interesting trip has been planned, assembling in Dallas. Leaving St. Louis the members will arrive at Staunton, Va., visit Monticello and other points in Virginia and arrive in Washington, May 7th. Leaving Washington after conclusion of the convention they will go to New York where they will be guests of the National Broadcasting studios for a full program and return by way of Canada to Chicago and visit the Century of Progress.

LEGAL AND LEGISLATIVE.

THE NEW COST DEFINITION.

"Inasmuch as the vast preponderance of drug store products are distributed to small drug retailers who are unable to purchase on a quantity basis but who perform services which are essential to the welfare of those in their communities, and whereas such services cannot adequately be performed through the facilities provided by their competitors, and whereas in some cases sales are made to consumers by such competitors at prices below the lowest cost of purchase normally obtainable for such merchandise by small drug retailers, and whereas in most instances such sales prices are not a true indication of the general level of prices of such competitors and no general benefit to those in the community accompanies the same, but such prices are in fact in the nature of bait offers of merchandise to attract trade.

"It is hereby declared unfair trade practice and is prohibited by this code for any drug retailer to sell any drugs, medicines, cosmetics, toilet preparations or drug sundries at a price below the *manufacturer's wholesale list price per dozen*, provided, however, that in the case of biological or other of the above-mentioned products which are not customarily sold in dozens or gross lots, the Code Authority may fix a comparable unit quantity, and provided further that any discount, free deal or rebate which is made available to all purchases of *dozen lots* or comparable quantities shall be considered as part of the manufacturer's wholesale list price."

NATIONAL RECOVERY ADMINISTRATION BEING TRANSFORMED TO CODE-ENFORCEMENT BODY.

The long proposed transformation of the National Recovery Administration from a code-making to a code-enforcing agency is definitely under way, but the objectives of using codes to increase employment while protecting labor and consumers remain prominent in NRA activities.

Tentative orders issued by Administrator Hugh S. Johnson not yet fully in effect completely reorganize the NRA, deputizing authority to lesser officials and providing machinery for quick disposal of complaints of violations of codes. The administrator will retain a veto power but each of the half-dozen divisions of the NRA will be largely autonomous and will have authority to dispose of all matters except those involving policies not definitely settled.

Reorganization of the NRA is being conducted by W. Averill Harriman, division administrator, temporarily in the capacity of first assistant to the administrator. Details of the NRA organization have become so voluminous that it is necessary to perfect an organization not so centered on the administrator personally as it has been to date. To this end each division will be made practically autonomous for purposes of code administration, each with its own group of legal, labor industrial and consumer advisors.

A new litigation division is being carved out of the legal division which will have the responsibility of bringing court actions against violators in cases where the code authorities have not been able to secure compliance with the code.—*Oil Paint and Drug Reporter.*

FIRMS MUST PAY NRA CODE COSTS OR FORFEIT EAGLE.

President Roosevelt, on April 14th, issued an order under which future display of the Blue Eagle will be allowed only to those firms which contribute to expenses of code administration, wherever such outlays are required.

To protect employers from racketeering by organizers of industrial groups, the President required that all Code Authority rates of assessments and budgets of expenditures must be approved by Administrator Hugh S. Johnson before any money can be collected.

The executive order does not command that every firm under every code pay dues, but substantially leaves this government-controlled method of financing administration the only avenue which may be followed.

Industries, under the order, will not be required to, but will have the right to apply to NRA for approval of a financing plan, which shall be put into effect if Administrator Johnson "shall find approval by him of such a clause is necessary."

Non-payment will constitute violation of the code, subject the firm involved to withdrawal of the Eagle, deprivation of all other code privileges and expose it to suit for collection on the part of the Code Authority.